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TABLE OF CONTENTS

ALCOHOL RESEARCH
Current Reviews

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From the Editors–Alcohol, Opioids, and Pain

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Opioids and alcohol are both effective analgesics under certain pain conditions. However, although the analgesic or pain-relieving properties of opioids are well known, information about the use of alcohol and its potential for misuse in the context of pain management has begun to emerge more recently. Alcohol doses required to alleviate pain are commensurate with binge drinking,[1] defined as drinking enough to achieve blood alcohol concentrations of 0.08 mg/dL or higher. Such pain-killing doses would typically occur after four drinks for women and five drinks for men in about 2 hours. Doses required for effective analgesia also are associated with unintentional injuries, violence, and traffic fatalities. Moreover, binge alcohol drinking over long periods to manage chronic pain also will foster profound negative health consequences, including organ damage and heightened cancer risk.[2]

After their initial pain-killing effects wear off, however, both alcohol and opioids, especially when used in high doses over long periods of time, can trigger opponent physiological responses that produce a temporary increase in pain sensitivity, known as hyperalgesia. These nociceptive processes reflect the unifying principle of homeostasis, the process by which complex physiological systems maintain biological stability. Simply put, what goes up must eventually come down to achieve a balanced resting state. With long-term heavy alcohol or opioid use, the opponent pro-nociceptive response grows, diminishing drug-induced analgesia (tolerance) while at the same time setting up a persistent sensory and emotional pain sensitization state that may occasion further drinking or opioid use, eventually heightening risk for the development of alcohol use disorder (AUD) or opioid use disorder (OUD) in vulnerable individuals. As such, understanding the AUD/OUD–pain relationship is among the most urgent public health challenges confronting us today.

Given the broad co-occurrence of hyperalgesia and AUD/OUD, pain may be best viewed as a core addiction phenotype. The view is supported by evidence acquired over the past decade that there is substantial overlap in brain circuitry and pathways underlying AUD, OUD, and pain centralization.[3] An improved understanding of the effects of alcohol on pain, the role of pain in alcohol misuse, and potential interactions between alcohol and opioids during pain treatment is an important step toward improved treatment outcomes for patients with chronic pain who are susceptible to AUD/OUD.

Pain is generally thought of as the unpleasant physical sensation following bodily harm or injury. Equally important, and mechanistically intertwined, is the psychological component of pain, particularly the emotional component of chronic and unrelieved pain. Mechanisms of neuroplasticity are thought

to underlie a "centralization of pain" at both spinal and supraspinal levels, and similar phenomena are used to describe how misused substances act on the brain to facilitate the development and maintenance of substance use disorder (SUD). In this topic series, Gilpin and colleagues describe functional changes in supraspinal circuits implicated in alcohol-induced changes in pain-related behavior ("Forebrain-Midbrain Circuits and Peptides in Hyperalgesia After Chronic Alcohol Exposure").[4] Their focus on interactions between midbrain and extended amygdala systems highlights novel avenues for managing pain in the context of AUD.

Alcohol or opioid misuse also can interact with pain to exacerbate negative emotional states (anhedonia, depression, and anxiety) as well as increase the sensitivity to such states (known as hyperkatifeia) to fuel continued or escalated substance use.[5] As with somatic pain, drinking alcohol or using opioids to cope with emotional pain only makes the situation worse. In their review, "The Convergent Neuroscience of Affective Pain and Substance Use Disorders," Pahng and Edwards describe contributions of stress-related signaling in key frontocortical brain areas to the dual and interactive manifestation of chronic pain and AUD/OUD symptomatology, highlighting research with refined animal models of these conditions.[6] In addition, economic and environmental sources of stress (such as social isolation and other anxieties associated with the COVID-19 pandemic) can further feed into this cycle, possibly contributing to increased alcohol drinking, opioid use, and suicide.[7] Within this theme, Zale and colleagues highlight transdiagnostic vulnerabilities in humans that are implicated across both maladaptive responses to pain (e.g., pain catastrophizing) and the motivation for alcohol and opioid use in their review, "Cognitive-Affective Transdiagnostic Factors Associated With Vulnerability to Alcohol and Prescription Opioid Use in the Context of Pain."[8]

Altogether, the reviews in this topic series represent the current state of neuroscience related to pain and AUD/OUD interactions spanning a wide range of research in both innovative animal models and humans. The translational efficacy of these directions will hinge largely on the continued collaborative efforts across health care professionals, multidisciplinary research laboratories, and National Institutes of Health institutes focused on these conditions. This topic series highlights many recent and exciting discoveries that will open up new conceptual avenues of research that may light the way ahead toward better treatment for both chronic pain and SUD.

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References

1. Thompson T, Oram C, Correll CU, Tsermentseli S, Stubbs B. Analgesic effects of alcohol: A systematic review and meta-analysis of controlled experimental studies in healthy participants. *J Pain.* 2017;18(5):499-510. https://doi.org/10.1016/j.jpain.2016.11.009.
2. Molina PE, Nelson S. Binge drinking's effects on the body. *Alcohol Res.* 2018;39(1):99-109.
3. Egli M, Koob GF, Edwards S. Alcohol dependence as a chronic pain disorder. *Neurosci Biobehav Rev.* 2012;36(10):2179-2192. https://doi.org/10.1016/j.neubiorev.2012.07.010.
4. Gilpin NW, Yu W, Kash TL. Forebrain-midbrain circuits and peptides involved in hyperalgesia after chronic alcohol exposure. *Alcohol Res.* 2021;41(1):13. https://doi.org/10.35946/arcr.v41.1.13.
5. Shurman J, Koob GF, Gutstein HB. Opioids, pain, the brain, and hyperkatifeia: A framework for the rational use of opioids for pain. *Pain Med*. 2010;11(7):1092-1098. https://doi.org/10.1111/j.1526-4637.2010.00881.x.
6. Pahng AR, Edwards S. The convergent neuroscience of affective pain and substance use disorders. *Alcohol Res.* 2021;41(1):14. https://doi.org/10.35946/arcr.v41.1.14.
7. Elman I, Borsook D, Volkow ND. Pain and suicidality: Insights from reward and addiction neuroscience. *Prog Neurobiol.* 2013;109:1-27. https://doi.org/10.1016/j.pneurobio.2013.06.003.
8. Zale EL, Powers JM, Ditre JW. Cognitive-affective transdiagnostic factors associated with vulnerability to alcohol and prescription opioid use in the context of pain. *Alcohol Res.* 2021;41(1):08. https://doi.org/10.35946/arcr.v41.1.08.

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The Convergent Neuroscience of Affective Pain and Substance Use Disorder

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Opioids and alcohol are widely used to relieve pain, with their analgesic efficacy stemming from rapid actions on both spinal and supraspinal nociceptive centers. As an extension of these relationships, both substances can be misused in attempts to manage negative affective symptoms stemming from chronic pain. Moreover, excessive use of opioids or alcohol facilitates the development of substance use disorder (SUD) as well as hyperalgesia, or enhanced pain sensitivity. Shared neurobiological mechanisms that promote hyperalgesia development in the context of SUD represent viable candidates for therapeutic intervention, with the ideal strategy capable of reducing both excessive substance use as well as pain symptoms simultaneously. Neurocognitive symptoms associated with SUD, ranging from poor risk management to the affective dimension of pain, are likely mediated by altered activities of key anatomical elements that modulate executive and interoceptive functions, including contributions from key frontocortical regions. To aid future discoveries, novel and translationally valid animal models of chronic pain and SUD remain under intense development and continued refinement. With these tools, future research strategies targeting severe SUD should focus on the common neurobiology between negative reinforcement and affective elements of pain, possibly by reducing excessive stress hormone and neurotransmitter activity within shared circuitry.

Keywords: alcohol; cingulate cortex; insula; opioids; pain; reinforcement

A central feature of substance use disorder (SUD) is the emergence of negative affective or emotional states that influence the motivational properties of misused substances.[1] Individual propensity to experience pain-related negative affect, for example, is hypothesized to be associated with the maintenance of both opioid use disorder (OUD) and alcohol use disorder (AUD). Chronic pain is estimated to affect approximately 20% of adults worldwide,[2] a number that will likely increase over

the next several decades given the aging global population. Accordingly, opioids and/or alcohol may be sought and taken in excessive amounts to alleviate such symptoms.[3,4] From a neuroanatomical perspective, ascending nociceptive circuitry is well known to interact with and alter the function of frontocortical reinforcement systems key to the development and maintenance of both OUD and AUD.[5] The current state of neuroscience research aims not only to understand how these interactions manifest in the brain, but also to exploit these discoveries to promote novel therapeutic strategies targeting both chronic pain and SUD.[6]

This review focuses on two widely used analgesic agents, opioids and alcohol. Excessive use of either substance generates neuroadaptations that likely contribute to negative reinforcement processes in which efforts to achieve pain relief intersect with the likelihood of developing SUD, sometimes known as SUD liability.[7] Historically, the majority of preclinical pain studies have focused on peripheral and spinal nociceptive processes, yet have produced few translational therapies for chronic pain or safe alternatives to opioid-based analgesia.[8] Although alcohol represents another widely utilized strategy for pain relief,[9] the many pathophysiological risks associated with heavy drinking considerably outweigh the analgesic benefits.[10]

The most recent conceptualizations and research efforts have attempted to understand the specific contributions of pain-associated negative affect to the establishment of a variety of SUD. These efforts have focused on the role of central nociceptive and motivational brain areas underlying the transition to chronic pain and its potentially crucial relationship to SUD.[11,12] From a neurobiological perspective, this review describes key contributions from frontocortical areas that represent a shared neuroanatomical substrate for the intersection of pain and SUD-related symptomatology. Although this review focuses on opioids and alcohol, it is important to note that other misused substances—including nicotine and cannabis—can act as analgesics, and integrative mechanisms described in this review may play a role in the manifestation of one or more types of SUD.

PAIN RELIEF AS NEGATIVE REINFORCEMENT IN SUD

Opioid analgesics are the most powerful and effective medications for the treatment of acute pain.[13] Opioids are also widely accepted for use with intractable pain related to cancer or end-of-life care. Both naturally occurring (e.g., morphine) and synthetic (e.g., fentanyl) opioids produce strong and quantifiable analgesia across multiple modalities in both humans and animal models. The opioid receptors (mu, kappa, and delta) differ by the endogenous ligands that bind to them and by the range of effects the receptors produce, which is largely dependent on receptor location.[14] The pain-relieving properties of opioids are predominately mediated by mu-opioid receptor function based on the high binding affinity of opioid analgesics to mu-opioid receptors; however, activities at both kappa- and delta-opioid receptors also mediate analgesia.[14,15] Opioid analgesics also can produce euphoria and reduce negative emotional states (e.g., stress, anxiety, depression), which is attributed to the high density of opioid receptors across limbic brain regions.[16] There is well-described evidence that acute alcohol administration also produces analgesia in both humans and animals, but to a lesser degree than opioids.[6] From a neuropharmacological perspective, alcohol analgesia relies on the engagement of endogenous opioid signaling,[17] but also involves additional mechanisms including G protein-activated inwardly rectifying potassium (GIRK) channel activity.[18] A meta-analysis by Thompson and colleagues found a strong linear relationship between alcohol consumption and reported analgesia in humans.[19] However, some limitations of the Thompson review should be noted, including its reliance on a limited number of studies (mostly in men) where effect sizes were collapsed across several pain modalities (thermal

and mechanical). Moreover, no patient groups were included in the reviewed studies, highlighting the urgent need for additional work in this clinical area. Analgesia was reported to be strongest with alcohol levels that exceed the National Institute on Alcohol Abuse and Alcoholism (NIAAA) definition of binge drinking.[20] This identifies the potential risk involved in consuming alcohol for analgesic purposes.[21] Furthermore, authors from an empirical study examining the interaction of pain and alcohol-induced analgesia found that hazardous drinkers (determined by AUDIT-C scores) had a greater urge and intention to drink alcohol when given experimentally induced pain compared to hazardous drinkers without pain induction.[22] This highlights an important motivational aspect of drug-induced analgesia, where acute pain can increase the desire to drink alcohol or take opioids as an active strategy for reducing pain and associated negative emotional states. For this reason, opioids and alcohol often may be used by some individuals for a combination of pain management and stress relief.

In contrast to acute pain treatment, there is limited evidence of the utility of opioid treatment for most chronic pain conditions aside from cancer pain or pain during end-of-life care.[23] There are also serious safety concerns that need to be considered when prescribing opioids for chronic pain, including risk of developing OUD as well as acute overdose and death; for more information, see the Centers for Disease Control and Prevention's guideline for prescribing opioids for chronic pain.[23] With regard to alcohol, Zale and colleagues describe a curvilinear association between drinking and pain outcomes.[24] Whereas low to moderate alcohol use is associated with analgesia, excessive drinking is associated with poorer pain trajectories over time.[24] Low to moderate drinking was defined as drinking below government cutoffs for hazardous or excessive drinking, while excessive drinking was defined as either binge (> 4 drinks in 2 hours for women; > 5 drinks in 2 hours for men) or heavy drinking (number of drinks on any day or per week; for women, > 3 and > 7, respectively; for men, > 4 and > 14, respectively).[24] As mentioned above, alcohol is an effective analgesic over a dose range that overlaps the NIAAA definition of "at-risk" or binge drinking limit (females, ≥ 4 drinks, and males, ≥ 5 drinks, in about 2 hours; https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/binge-drinking).[19] If individuals limit their drinking below this point, they may achieve some analgesic efficacy with a reduced risk of later poor health outcomes. However, if they cross this line (perhaps to achieve greater analgesia), it places them at risk of eventually developing AUD and emerging hyperalgesia symptoms.

One key reason for the increasing use of opioids and alcohol for pain relief is the development of analgesic tolerance with repeated and/or extensive use. Tolerance refers to the principle that higher dose amounts of a substance are necessary to maintain the same biochemical and perceptual effects over time,[25] which both complicates treatment regimens and heightens SUD risk. A small prospective clinical study examined the effects of short-term opioid use on analgesic tolerance and pain sensitivity in the context of chronic pain.[26] Thermal pain thresholds and pain tolerance were assessed in individuals with chronic lower back pain, both before and after 1 month of an escalating oral morphine treatment regimen. A short-acting opioid was given prior to pain testing to examine changes to the analgesic efficacy of opioids following this 1 month of morphine treatment. Under this state, there was a significant decrease in pain thresholds and tolerance on the cold pressor test (measure of cold pain sensitivity), but no effects on heat-related pain. The rapid development of analgesic tolerance to opioids adds support to the limited clinical effectiveness of using opioids for long-term pain treatment. Tolerance to the analgesic and euphoric effects of opioids develops faster than tolerance to other physiological symptoms, including respiratory depression.[27] This explains why the risk of respiratory depression increases with escalated opioid use or in those who formerly misused opioids heavily and renewed opioid use after a period of protracted abstinence.

The development of analgesic tolerance following chronic alcohol exposure also has been well described in animal research,[6,17,28] but there is a lack of empirical human trials investigating the impact of tolerance on alcohol's analgesic effects.[24] Also unknown is how analgesic tolerance promotes alcohol craving or escalation of alcohol use in attempts to maintain analgesic effects over time.

Excessive use of alcohol and/or opioids may lead to states where both analgesic tolerance and hyperalgesia symptoms coincide.[29] Hyperalgesia is a form of pronociceptive system sensitization that behaviorally manifests as heightened pain sensitivity. Analgesic tolerance, along with the consequent escalation of analgesic use, contributes to the development of hyperalgesia, and are all hallmarks of opioid and alcohol dependence. In an opioid- and alcohol-dependent state, abstinence results in somatic withdrawal signs, pain, negative affect, and drug craving. These negative consequences can drive escalation of use over time, where negative reinforcement is the primary motivator for continued use or renewal during relapse.[1] Carcoba and colleagues examined the role of negative affect in opioid withdrawal-induced hyperalgesia in heroin-dependent individuals.[30] Compared to healthy controls, individuals in acute withdrawal (24 to 72 hours) and those in protracted withdrawal (~ 30 months) from heroin exhibited decreased pain thresholds and tolerance during an ischemic pain procedure. These hyperalgesic effects were heightened by viewing negative pictures (International Affective Picture System) beforehand, which elicit negative emotional states. Opioid-enhanced pain sensitivity can also play a role in cue-induced opioid craving following protracted abstinence. In another study, the cold pressor test was used to examine pain responses in abstinent individuals with a history of OUD.[31] These individuals had shorter periods of pain tolerance and reported higher ratings of pain-related distress compared to healthy controls. There was also a positive association between pain-related distress and opioid craving. In a cross-sectional study, individuals undergoing medication-assisted treatment (MAT) with methadone or buprenorphine were examined for opioid craving and recent illicit opioid use.[32] The investigators found that chronic pain was present in 68% of the sample and was associated with threefold higher odds of reporting craving, potentially placing this population at greater risk of relapse. Similarly, in a separate study, chronic pain levels at baseline were correlated with lower pain tolerance, greater stress reactivity during a cold pressor task, and posttest levels of opioid craving in individuals with comorbid pain and OUD.[33] Within comorbid pain and OUD groups, individuals who currently or formerly used MAT for OUD demonstrated increases in stress-reactivity to pain compared to opioid-naïve individuals with chronic pain. Furthermore, abstinent individuals who formerly used MAT for OUD demonstrated increased stress-reactivity to pain for some measures compared to current MAT users, indicating long-lasting consequences of OUD on neurophysiological outcomes.

Similar to opioids, hyperalgesia induced by alcohol withdrawal contributes to alcohol misuse and the development of AUD.[6] There are strong associations between alcohol consumption, pain, and pain-related disability.[34,35] In a secondary analysis of two clinical trials, Witkiewitz and colleagues found that greater pain scores were associated with alcohol drinking and increases in negative affect 1 year after treatment for AUD.[36] Using another large clinical data set, Yeung and colleagues examined the relationship between alcohol and pain interference (i.e., how pain interferes with everyday life).[35] In this analysis, higher alcohol consumption at baseline was associated with lower pain interference at 1-year follow-up. However, the opposite was true for individuals who exhibited more AUD symptoms. For them, higher baseline alcohol consumption was significantly related to higher pain interference at 1-year follow-up, indicating that the detrimental effects of alcohol on pain interference may emerge as the severity of the disease progresses. There is also a strong association between alcohol consumption, chronic pain, and pain-associated disability. Among persons with chronic pain, disabling pain was strongly associated with their

level of alcohol consumption.[37] There is some evidence that chronic pain status may be predictive of future drug and alcohol use. In prospective epidemiological studies, self-reported pain interference was predictive of AUD development,[38] and persistent pain was associated with increased odds of opioid use (adjusted odds ratio [*AOR*] = 5.4) and heavy alcohol use (*AOR* = 2.2) compared to no pain.[39]

With human research, it is very difficult to determine the direction of causality for the relationship between SUD and pain. Fortunately, a major benefit of animal research is the care with which experimental conditions can be controlled to determine the direction of causality for these complex associations. Preclinical animal research has been critical for the modeling of interactions between pain and SUD, and some of the most widely used techniques are described here.

ANIMAL MODELS TO EXAMINE PAIN AND SUD INTERACTIONS

Key symptomatology of OUD and AUD—including escalation of drug intake, compulsive drug seeking, development of hyperalgesia, and the emergence of negative affective states—can be reliably modeled in rodents. When discussing drug-induced hyperalgesia, it is necessary to discriminate that nociception and pain are different phenomena. Nociception refers to the neural process of encoding noxious stimuli, whereas pain refers to a personal experience that is influenced by biological, psychological, and social factors. Pain is therefore a subjective and inherently emotional experience. Accordingly, the empirical assessment of pain in rodents can be challenging. It is possible, however, to assess nociception and affective pain-like behavior in rodents through a variety of assays. Preclinical animal models also provide valuable tools for investigating the somatic and behavioral symptoms of SUD, identifying neurobiological changes associated with SUD, and testing medications to alleviate symptoms of dependence and reduce abuse liability. These models impact medication development and increase understanding of the behaviors that contribute to the development of SUD. There are several different procedures for inducing opioid and alcohol dependence in animals. Most involve the general procedure of repeatedly putting animals through a period of intoxication where the drug is administered by the experimenter or self-administered by the animals. This is followed by a period where the drug is not available, which produces a state of spontaneous withdrawal. As this cycle of intoxication and withdrawal is repeated, animals will begin to exhibit symptoms of dependence, including escalation of intake (if the drug is self-administered), pain-like behavior, compulsive drug-seeking behavior, and the emergence of negative emotional states (e.g., anxiety-like behavior).[40] When the drug is administered by the experimenter, the behavioral and neurochemical consequences of drug escalation can be mimicked by giving animals an escalating dose regimen to achieve a state of dependence.[40] In rodents, the most commonly used routes of administration for opioids include intravenous self-administration and subcutaneous administration, while the routes of administration for alcohol include oral self-administration, ethanol vapor exposure, intragastric gavage, a liquid diet containing alcohol (e.g., Lieber-DeCarli diet), and intraperitoneal administration.

Measurement of Nociception and Affective Pain in Animals

There are numerous tests to assay pain-like behavior in rodent models of psychiatric disease,[41] although the most common tests of nociceptive behavior in the context of hyperalgesia include von Frey[42] and Hargreaves[43] tests of mechanical hypersensitivity and thermal hypersensitivity, respectively. These reflexive-based tests involve applying a mechanical or thermal stimulus to the rodent's hind paw and measuring either the paw withdrawal threshold (typically in grams of pressure) for a graded mechanical stimulus or the paw withdrawal latency (typically in seconds)

for a constant thermal stimulus. A higher paw withdrawal threshold or latency compared to baseline is associated with an analgesic or anti-nociceptive process (e.g., following administration of an opioid substance), while a lower paw withdrawal threshold or latency is associated with hyperalgesia (i.e., more sensitive to the stimulus when compared to baseline). As discussed earlier, the subjective pain experience can greatly impact motivational processes associated with the transition to SUD. One shortcoming of these reflexive-based assays is the inability to assess the motivational and affective dimensions of pain, which are hypothesized to influence the transition to both chronic pain states[44] and SUD.[45,46] Neuroscientists are beginning to employ additional behavioral tests that attempt to more closely assess the cognitive and motivational aspects of pain-like behavior beyond the somatic or sensory components. These non-reflexive-based assays allow the potential to examine the contribution of negative affective-like states towards activity avoidance and pain interference in the context of SUD.[47,48] In the mechanical conflict-avoidance system (MCS) task, animals traverse mechanically noxious probes of varying heights to avoid a bright aversive light, escaping to reach a goal chamber that is dark. A longer latency to exit onto the probes reflects increased pain avoidance-like behavior as a motivational correlate of hyperalgesia. The specific strengths and limitations of the MCS procedure have been described, illustrating its utility in measuring both analgesic and hyperalgesic conditions.[47,49,50] Another innovative technique in this area is the Orofacial Pain Assessment Device (OPAD), which pairs a thermal stimulus conflict with access to an appetitive reward[51] and can be readily applied to oral alcohol or opioid self-administration. These reflex-based and non-reflex-based pain assays can be used in tandem to more comprehensively examine the effects of opioid and alcohol dependence on both somatic and affective pain-like behaviors in rodents.

Measurement of Opioid-Induced Hyperalgesia in Animals

Induction of opioid dependence in rodents can be achieved through intravenous self-administration where animals are given extended (or long) access (LgA; 6 hr, 12 hr, or 24 hr) versus limited (or short) access (ShA, 1 hr) to opioids,[52] including prescription opioids such as fentanyl and oxycodone.[53] In this model, LgA animals exhibit hallmarks of OUD including escalation of opioid intake, compulsive opioid seeking, development of hyperalgesia, and the emergence of negative emotional states. Male Wistar rats given LgA (12 hr) to heroin self-administration (0.06 mg/kg/infusion) exhibit decreased paw withdrawal thresholds compared to ShA (1 hr) animals during spontaneous withdrawal, indicating opioid-induced mechanical hyperalgesia.[54] Interestingly, the emergence of opioid-induced hyperalgesia coincided with escalated heroin intake in LgA animals, which was not observed in ShA animals.[54] In this study, increased heroin intake was significantly correlated with increased pain-like behavior (lower paw withdrawal thresholds), demonstrating the close relationship between opioid intake and pain symptoms in the context of dependence. Repeated subcutaneous administration of opioids can also induce dependence and pain-like behavior in rodents. Rats given repeated subcutaneous doses of heroin for 5 days exhibited decreased paw withdrawal thresholds compared to animals given a single dose of heroin, demonstrating the ability of opioids to drive nociceptive system sensitization.[29] In a separate study, male Wistar rats were given an escalating dose regimen of morphine (10 mg/kg to 20 mg/kg) over 2 weeks to examine the effects of morphine dependence on the sensory and motivational/affective components of pain-like behavior, using von Frey and MCS procedures, respectively.[49] Opioid-dependent animals exhibited an increased latency to exit onto a bed of noxious mechanical probes during withdrawal compared to saline-injected controls, indicating increased pain-like

avoidance with escalated morphine use. There was a modest but significant correlation between changes in mechanical hypersensitivity and pain-like avoidance behavior, indicating that the von Frey and MCS procedures examine overlapping, but not identical, measures of pain-like behavior. Continued investigations that shed light on individual differences in opioid and pain sensitivity along both somatic and affective dimensions also may help researchers to maximize the beneficial use of opioid analgesics while minimizing OUD liability.

Measurement of Alcohol-Induced Hyperalgesia in Animals

The somatic and affective symptoms of AUD can be reliably modeled in rodents using chronic intermittent ethanol vapor (CIEV) exposure.[55] The intermittent procedure involves daily cycles of alcohol vapor (producing peak blood alcohol levels of 150–200 mg/dl) and alcohol withdrawal. After several weeks of CIEV, alcohol-dependent male Wistar rats exhibited decreases in paw withdrawal thresholds during spontaneous withdrawal compared to non-dependent controls, indicating alcohol-induced mechanical hyperalgesia.[54] In a separate study, 4 weeks of CIEV produced thermal hyperalgesia in alcohol-dependent male Wistar rats compared to nondependent controls.[56] This increase in pain-like behavior was attenuated following either alcohol administration by the experimenter or alcohol self-administration. The anti-hyperalgesic effects of acute alcohol treatment in alcohol dependence provides strong evidence of the motivation to drink alcohol to ameliorate withdrawal symptoms and decrease pain. In a nonforced contingent ethanol vapor self-administration study, male Wistar rats were allowed to nose poke for ethanol vapor (8 hr/day) over either 8 or 24 sessions, which produced nonescalated and escalated nose poking for ethanol vapor exposure, respectively.[57] Like the previous CIEV studies, rodents who escalated nose pokes demonstrated decreased paw withdrawal thresholds during withdrawal compared to nonescalated animals, indicating increased pain-like behavior. Additional models of alcohol dependence, including chronic intermittent two-bottle choice and the Lieber–DeCarli diet, produced mechanical and thermal hyperalgesia in male Sprague Dawley rats,[58,59] and the "Drinking in the Dark" procedure facilitated hyperalgesia in female and male C57BL/6J mice.[60]

Examining How Pain Influences Opioid and Alcohol Use in Animals

Another interesting area of preclinical pain research involves examining the effects of persistent pain on drug abuse liability. Neuropathic pain, fibromyalgia, low back pain, and osteoarthritis are common medical conditions that contribute to the burden of chronic pain disorders. Accordingly, preclinical models of neuropathic pain (e.g., spared nerve injury, spinal nerve ligation) and inflammatory pain (e.g., complete Freund's adjuvant [CFA]) are frequently used to examine the effects of chronic pain on behavior and neurochemistry in rodents. Martin and colleagues found that, compared to controls, nerve-injured male Fisher 344 rats required higher amounts of heroin to maintain heroin self-administration and were more sensitive to mu-opioid receptor antagonist-induced increases in heroin self-administration.[61] In a study examining how persistent inflammatory pain alters morphine preference, CFA reduced the number of morphine conditioning sessions required to acquire morphine-conditioned place preference in male Wistar rats.[62] Hipólito and colleagues found that CFA altered heroin self-administration in a dose-dependent manner in male Sprague Dawley rats.[63] High unit doses (0.2 mg/kg/infusion) were more reinforcing, and low unit doses (0.05 mg/kg/infusion) were less reinforcing. These preclinical examinations provide evidence for the hypothesis that the driving force for motivation to self-administer opioids in individuals with an underlying pain condition may be in part to seek relief from chronic pain. These findings may also indicate that shared neural substrates promote both substance use and pain chronification, or the process by which acute pain becomes chronic, as discussed in the next section.

A number of additional studies have examined the effects of chronic pain on alcohol consumption

in rodents.[64] Sciatic nerve–injured CD1 male mice consumed more alcohol (20% ethanol) and exhibited increased anxiety-like behavior compared to sham-operated mice, suggesting that a chronic pain state drives increased alcohol consumption.[65] In a mouse model of osteoarthritis, male C57BL/6J mice consumed significantly more alcohol than sham controls during a two-bottle choice test of escalating alcohol concentrations (2.5% to 20%).[66] During a 20% ethanol continuous access test, CFA increased alcohol drinking in male C57BL/6J mice, but did not increase drinking in female C57BL/6J mice.[67] In contrast to these findings in mice, a recent study found no effect of CFA on alcohol self-consumption or alcohol preference in male Wistar rats.[68] However, this study discovered that the relationship between alcohol drinking levels and hyperalgesia symptoms reversed between acute (1-week) and chronic (3-week) periods post-CFA administration, suggesting that either the motivational or analgesic effects of alcohol may be altered over the time course of chronic pain.

Altogether, there appear to be clear effects of chronic pain on opioid intake, motivation for opioids, alcohol consumption, and alcohol preference that are largely dependent on factors including rodent species and sex. In summary, repeated and extensive exposure to opioids and alcohol promotes escalation of intake and pain-like behavior, which are sequelae that can in turn exacerbate abuse liability and SUD disease severity.

SHARED FRONTOCORTICAL SUBSTRATES FOR AFFECTIVE PAIN AND SUD

In addition to somatosensory elements, both affective/emotional and cognitive/motivational dimensions can augment pain-related morbidity.[6] Chronic pain can generate continual negative affective states and promote new cognitive strategies and behaviors to avoid pain. Consequently, pain relief itself activates reward circuitry and is experienced as a positively valenced emotional state.[69] It is thus hypothesized that the emergence of painful states following chronic or excessive opioid or alcohol exposure facilitates negative reinforcement processes whereby individuals seek relief from pain by escalating use of these substances, culminating in the development of psychiatric sequelae including SUD.[45,46] Specific alterations in frontocortical activity may facilitate pain and promote maladaptive behaviors in close association with pain-related negative affective states. As such activity is heavily impacted by chronic or excessive opioid and alcohol exposure, further interrogation of within- and between-circuit neuroadaptations is warranted to better understand the pathological intersection of pain and SUD.[46,70]

INSULAR AND CINGULATE CORTICES AND AFFECTIVE PAIN PROCESSING

The insular cortex and the cingulate cortex represent key components of a distinct neural network within the larger executive control system of the prefrontal cortex. Communication within these areas is hypothesized to facilitate attribution of emotional salience to both internal and external stimuli, including pain-related noxious stimuli.[9] Of particular interest is the role of frontocortical regions in higher nociceptive processing, as well as their historical association with SUD.[5] Pain is a multidimensional experience, which comprises both sensory and affective-motivational components.[71] Through studies of these regions both in isolation and as a functional network, the insula and cingulate have been identified as key areas for supraspinal processing of the affective dimension.[18] Imaging studies have also identified heightened activity in the insula and cingulate with the anticipation of pain and have correlated perceived pain intensity with degree of concurrent activity in the insula and cingulate in human subjects.[72,73] In rodent models, selective lesions of the cingulate have been shown to reduce pain-related aversion without altering the sensory element of noxious stimuli.[74,75] The insula has reciprocal connections with the cingulate and receives nociceptive

information directly from the thalamus.[76] Moreover, insula connectivity with subcortical regions such as the amygdala may facilitate emotional arousal to noxious stimuli.[76,77]

Resting-state functional magnetic resonance imaging (fMRI) analyses have identified a precise network based in the insula and cingulate that extends to several subcortical regions referred to as the salience network. The salience network model was developed from the integration of multiple human fMRI studies that ultimately led to the hypothesis that this particular circuitry recognizes and assimilates interoceptive and external information, recruits and derecruits additional executive networks to engage the appropriate cognitive processes (focusing attention to stimuli, including noxious stimuli), and ultimately regulates an adaptive behavioral response.[78] Alterations in the salience network are observed in individuals with chronic pain and are associated specifically with greater pain catastrophizing,[79] a phenomenon that is believed to be closely related to the chronification of pain. The network has most commonly been investigated in human and nonhuman primate models, but was recently confirmed in rodents, validating crucial contributions from the insula and cingulate cortex.[80]

DYSREGULATION OF THE SALIENCE NETWORK BY ALCOHOL AND OPIOIDS

Research has provided evidence that AUD dysregulates activity of the insula-cingulate salience network in humans, typically indicated by fMRI analyses. This alteration is believed to impair executive function, compromising the ability to make appropriate or cognitively demanding decisions.[81] Salience network deficits may specifically contribute to the maintenance or exacerbation of AUD by making an individual unable to clearly discern risky behaviors, such as the decision to seek out and consume excessive amounts of alcohol despite adverse consequences. This network may be particularly vulnerable in AUD patients exposed to stressful conditions due to cingulate dysfunction.[82] Investigators have also found that excessive drinking may disrupt normal associations between interoception and pain.[83] A similar involvement of endogenous opioid signaling in salience network function is well known.[84] Alterations in the network's connectivity are related to resting state dysfunction[85] as well as to relapse behaviors[86] in patients with OUD. More studies are needed to examine salience network activity in populations with OUD in relation to hyperalgesia symptoms, especially because pain symptoms can promote opioid craving even after months of abstinence.[31]

Although the salience network is most commonly examined in humans, several preclinical animal studies have begun to examine the importance of this construct with relation to pain and alcohol exposure. Interestingly, in mice, the insula and cingulate were discovered to have a role in the social transfer of pain associated with hyperalgesia following alcohol withdrawal.[87] Another recent study found several interbrain regional correlations of glucocorticoid receptor (GR) phosphorylation in animals experiencing a binge alcohol withdrawal episode in the context of chronic inflammatory pain.[68] The insular cortex acted as a hub for these correlations with other nociceptive regions investigated (including the cingulate cortex and central amygdala), suggesting coordinated activity in insula circuitry and glucocorticoid signaling in the context of pain and alcohol withdrawal. This type of within-subject molecular analysis at the animal level may model human fMRI analyses of related network activity. These circuit-based relationships also have been hypothesized to play a key role in the motivational processes relevant to SUD.[5] Finally, a recent conceptual review postulated that neurovisceral feedback and interoceptive dysregulation by opioids and alcohol can be traced to alterations in gut microbiota,[88] highlighting the need for further investigation of the gut-brain axis in SUD and related pain.

BRAIN STRESS SIGNALING IN AFFECTIVE PAIN AND SUD

Given that chronic and unmitigated pain represents a significant stressor, elucidation of chronic opioid- and alcohol-induced neuroadaptations within brain stress systems may provide valuable insights into potential mechanisms underlying the transition to SUD in vulnerable individuals. Indeed, the role of central stress hormone and neuropeptide signaling in response to stress has emerged as a conceptual bridge between chronic substance use, affective and cognitive disruption, and propensity to relapse.[89] As the key integrative link between the systemic and central brain stress response, the hypothalamic-pituitary-adrenal (HPA) axis is responsible for orchestrating adaptive processes that return an organism to homeostasis following exposure to a stressor. Release of corticotropin-releasing factor (CRF) from the hypothalamus initiates this process by regulating the production and processing of pro-opiomelanocortin from the anterior pituitary. The pro-opiomelanocortin transcript produces two key peptides related to the effective management of both stress (adrenocorticotropic hormone) and pain (beta-endorphin), illustrating the close relationships between these two vital physiological systems. Adrenocorticotropic hormone acts to facilitate the production and release of glucocorticoids from the adrenal cortex, after which the systemic response is under the control of critical negative and positive feedback mechanisms, whereby glucocorticoids can inhibit or stimulate (respectively) their own genomic and nongenomic actions by binding to GRs in the brain.[90] Stress sensitization via potentiated GR signaling may represent one mechanism for intensification of SUD-associated negative affective symptoms, termed hyperkatifeia.[46]

Alcohol-dependent animals display a functional increase in brain GR signaling that appears to emerge during the transition to dependence.[91] GR antagonism reduces escalated drinking in both preclinical animal models and in individuals suffering from AUD.[92] It is also interesting that systemic administration of the GR antagonist mifepristone alleviates mechanical hyperalgesia symptoms observed in animals fed an alcohol diet.[93] These convergent findings suggest that targeting excessive stress signaling may be capable of treating both excessive drinking and pain symptoms in the context of AUD. Less is understood about these associations in relation to OUD, although similar relationships connecting negative reinforcement processes to pain and OUD have been proposed.[94,95] These conceptualizations are supported by research indicating links between serum cortisol levels and opioid withdrawal in humans[96] and functional activation of negative reinforcement brain centers in opioid-dependent animals.[97] Although systemic CRF_1 receptor antagonism has been shown to alleviate hyperalgesia symptoms in opioid-dependent animals,[54] no studies have investigated the potential contribution of GR signaling in this process. Given the role of chronic stress and glucocorticoid activity in exacerbating pain,[98] additional work is necessary to determine the relationships between stress hormone signaling and pain symptoms in patients suffering from AUD and OUD.

CONCLUSIONS

Few effective therapies exist for SUD or chronic pain. The accretive pathophysiology and shared neurobiological interactions of these disease states likely complicate their effective treatment. Powerful reinforcement processes maintain the use of opioids and alcohol to manage pain as well as the negative affective states that underlie chronic pain experiences. Future translational research priorities should aim to bridge gaps in our understanding of how opioids and alcohol act on nociceptive and higher motivational circuitry to drive tolerance and hyperalgesia symptoms that may exacerbate SUD. Numerous symptoms are regularly associated with severe SUD, ranging from poor risk management to the cognitive/affective dimension of pain. These symptoms are likely driven by neuroadaptations within key anatomical elements that regulate higher

executive functions, including key contributions from the cingulate and insula cortices.

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References

1. Edwards S, Koob GF. Neurobiology of dysregulated motivational systems in drug addiction. *Future Neurol.* 2010;5(3):393-401. https://doi.org/10.2217/fnl.10.14.
2. Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health.* 2011;11:770. https://doi.org/10.1186/1471-2458-11-770.
3. Riley JL 3rd, King C. Self-report of alcohol use for pain in a multi-ethnic community sample. *J Pain.* 2009;10(9):944-952. https://doi.org/10.1016/j.jpain.2009.03.005.
4. Ditre JW, Zale EL, LaRowe LR. A reciprocal model of pain and substance use: Transdiagnostic considerations, clinical implications, and future directions. *Annu Rev Clin Psychol.* 2019;15:503-528. https://doi.org/10.1146/annurev-clinpsy-050718-095440.
5. George O, Koob GF. Individual differences in prefrontal cortex function and the transition from drug use to drug dependence. *Neurosci Biobehav Rev.* 2010;35(2):232-247. https://doi.org/10.1016/j.neubiorev.2010.05.002.
6. Egli M, Koob GF, Edwards S. Alcohol dependence as a chronic pain disorder. *Neurosci Biobehav Rev.* 2012;36(10):2179-2192. https://doi.org/10.1016/j.neubiorev.2012.07.010.
7. Delery EC, Edwards S. Neuropeptide and cytokine regulation of pain in the context of substance use disorders. *Neuropharmacology.* 2020;174:108153. https://doi.org/10.1016/j.neuropharm.2020.108153.
8. Yezierski RP, Hansson P. Inflammatory and neuropathic pain from bench to bedside: What went wrong? *J Pain.* 2018;19(6):571-588. https://doi.org/10.1016/j.jpain.2017.12.261.
9. Thompson JM, Neugebauer V. Cortico-limbic pain mechanisms. *Neurosci Lett.* 2019;702:15-23. https://doi.org/10.1016/j.neulet.2018.11.037.
10. Molina PE, Nelson S. Binge drinking's effects on the body. *Alcohol Res.* 2018;39(1):99-109.
11. Elman I, Borsook D, Volkow ND. Pain and suicidality: Insights from reward and addiction neuroscience. *Prog Neurobiol.* 2013;109:1-27. https://doi.org/10.1016/j.pneurobio.2013.06.003.
12. Edwards S, Vendruscolo LF, Gilpin NW, Wojnar M, Witkiewitz K. Alcohol and pain: A translational review of preclinical and clinical findings to inform future treatment strategies. *Alcohol Clin Exp Res.* 2020;44(2):368-383. https://doi.org/10.1111/acer.14260.
13. Corder G, Castro DC, Bruchas MR, Scherrer G. Endogenous and exogenous opioids in pain. *Annu Rev Neurosci.* 2018;41:453-473. https://doi.org/10.1146/annurev-neuro-080317-061522.
14. James A, Williams J. Basic opioid pharmacology–an update. *Br J Pain.* 2020;14(2):115-121. https://doi.org/10.1177/2049463720911986.
15. Jordan BA, Cvejic S, Devi LA. Opioids and their complicated receptor complexes. *Neuropsychopharmacology. 2000;23*(4 suppl): S5-S18. https://doi.org/10.1016/S0893-133X(00)00143-3.
16. Lutz PE, Kieffer BL. Opioid receptors: Distinct roles in mood disorders. *Trends Neurosci.* 2013;36(3):195-206. https://doi.org/10.1016/j.tins.2012.11.002.
17. Neddenriep B, Bagdas D, Contreras KM, et al. Pharmacological mechanisms of alcohol analgesic-like properties in mouse models of acute and chronic pain. *Neuropharmacology.* 2019;160:107793. https://doi.org/10.1016/j.neuropharm.2019.107793.
18. Ikeda K, Kobayashi T, Kumanishi T, Yano R, Sora I, Niki H. Molecular mechanisms of analgesia induced by opioids and ethanol: Is the GIRK channel one of the keys? *Neurosci Res.* 2002;44(2):121-131. https://doi.org/10.1016/s0168-0102(02)00094-9.
19. Thompson T, Oram C, Correll CU, Tsermentseli S, Stubbs B. Analgesic effects of alcohol: A systematic review and meta-analysis of controlled experimental studies in healthy participants. *J Pain.* 2017;18(5):499-510. https://doi.org/10.1016/j.jpain.2016.11.009.
20. National Institute on Alcohol Abuse and Alcoholism. Drinking Levels Defined. No date. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking.
21. Cucinello-Ragland JA, Edwards S. Neurobiological aspects of pain in the context of alcohol use disorder. *Int Rev Neurobiol.* 2021;157:1-29. https://doi.org/10.1016/bs.irn.2020.09.001.
22. Moskal D, Maisto SA, De Vita M, Ditre JW. Effects of experimental pain induction on alcohol urge, intention to consume alcohol, and alcohol demand. *Exp Clin Psychopharmacol.* 2018;26(1):65-76. https://doi.org/10.1037/pha0000170.
23. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA.* 2016;315(15):1624-1645. https://doi.org/10.1001/jama.2016.1464.
24. Zale EL, Maisto SA, Ditre JW. Interrelations between pain and alcohol: An integrative review. *Clin Psychol Rev.* 2015;37:57-71. https://doi.org/10.1016/j.cpr.2015.02.005.
25. Mercadante S, Arcuri E, Santoni A. Opioid-induced tolerance and hyperalgesia. *CNS Drugs.* 2019;33(10):943-955. https://doi.org/10.1007/s40263-019-00660-0.
26. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: A preliminary prospective study. *J Pain.* 2006;7(1):43-48. https://doi.org/10.1016/j.jpain.2005.08.001.
27. Martyn JAJ, Mao J, Bittner EA. Opioid tolerance in critical illness. *N Engl J Med.* 2019;380(4):365-378. https://doi.org/10.1056/NEJMra1800222.
28. Elvig SK, McGinn MA, Smith C, Arends MA, Koob GF, Vendruscolo LF. Tolerance to alcohol: A critical yet understudied factor in alcohol addiction. *Pharmacol Biochem Behav.* 2021;204:173155. https://doi.org/10.1016/j.pbb.2021.173155.

29. Park PE, Schlosburg JE, Vendruscolo LF, Schulteis G, Edwards S, Koob GF. Chronic CRF_1 receptor blockade reduces heroin intake escalation and dependence-induced hyperalgesia. *Addict Biol.* 2015;20(2):275-284. https://doi.org/10.1111/adb.12120.
30. Carcoba LM, Contreras AE, Cepeda-Benito A, Meagher MW. Negative affect heightens opiate withdrawal-induced hyperalgesia in heroin dependent individuals. *J Addict Dis.* 2011;30(3):258-270. https://doi.org/10.1080/10550887.2011.581985.
31. Ren ZY, Shi J, Epstein DH, Wang J, Lu L. Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving. *Psychopharmacology (Berl).* 2009;204(3):423-429. https://doi.org/10.1007/s00213-009-1472-0.
32. Tsui JI, Lira MC, Cheng DM, et al. Chronic pain, craving, and illicit opioid use among patients receiving opioid agonist therapy. *Drug Alcohol Depend.* 2016;166:26-31. https://doi.org/10.1016/j.drugalcdep.2016.06.024.
33. Wachholtz A, Gonzalez G, Ziedonis D. Psycho-physiological response to pain among individuals with comorbid pain and opioid use disorder: Implications for patients with prolonged abstinence. *Am J Drug Alcohol Abuse.* 2019;45(5):495-505. https://doi.org/10.1080/00952990.2019.1620260.
34. Witkiewitz K, Vowles KE, McCallion E, Frohe T, Kirouac M, Maisto SA. Pain as a predictor of heavy drinking and any drinking lapses in the COMBINE study and the UK Alcohol Treatment Trial. *Addiction.* 2015;110(8):1262-1271. https://doi.org/10.1111/add.12964.
35. Yeung EW, Lee MR, McDowell Y, Sher KJ, Gizer IR. The association between alcohol consumption and pain interference in a nationally representative sample: The moderating roles of gender and alcohol use disorder symptomatology. *Alcohol Clin Exp Res.* 2020;44(3):645-659. https://doi.org/10.1111/acer.14282.
36. Witkiewitz K, McCallion E, Vowles KE, et al. Association between physical pain and alcohol treatment outcomes: The mediating role of negative affect. *J Consult Clin Psychol.* 2015;83(6):1044-1057. https://doi.org/10.1037/ccp0000033.
37. Macfarlane GJ, Beasley M. Alcohol consumption in relation to risk and severity of chronic widespread pain: Results from a UK population-based study. *Arthritis Care Res (Hoboken).* 2015;67(9):1297-1303. https://doi.org/10.1002/acr.22604.
38. McDermott KA, Joyner KJ, Hakes JK, Okey SA, Cougle JR. Pain interference and alcohol, nicotine, and cannabis use disorder in a national sample of substance users. *Drug Alcohol Depend.* 2018;186:53-59. https://doi.org/10.1016/j.drugalcdep.2018.01.011.
39. Larson MJ, Paasche-Orlow M, Cheng DM, Lloyd-Travaglini C, Saitz R, Samet JH. Persistent pain is associated with substance use after detoxification: A prospective cohort analysis. *Addiction.* 2007;102(5):752-760. https:/doi.org/10.1111/j.1360-0443.2007.01759.x.
40. Edwards S. Reinforcement principles for addiction medicine; from recreational drug use to psychiatric disorder. *Prog Brain Res.* 2016;223:63-76. https://doi.org/10.1016/bs.pbr.2015.07.005.
41. Bravo L, Llorca-Torralba M, Suarez-Pereira I, Berrocoso E. Pain in neuropsychiatry: Insights from animal models. *Neurosci Biobehav Rev.* 2020;115:96-115. https://doi.org/10.1016/j.neubiorev.2020.04.029.
42. Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL. Quantitative assessment of tactile allodynia in the rat paw. *J Neurosci Methods.* 1994;53(1):55-63. https://doi.org/10.1016/0165-0270(94)90144-9.
43. Hargreaves K, Dubner R, Brown F, Flores C, Joris J. A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain.* 1988;32(1):77-88. https://doi.org/10.1016/0304-3959(88)90026-7.
44. Schutze R, Rees C, Smith A, Slater H, Campbell JM, O'Sullivan P. How can we best reduce pain catastrophizing in adults with chronic noncancer pain? A systematic review and meta-analysis. *J Pain.* 2018;19(3):233-256. https://doi.org/10.1016/j.jpain.2017.09.010.
45. LeBlanc DM, McGinn MA, Itoga CA, Edwards S. The affective dimension of pain as a risk factor for drug and alcohol addiction. *Alcohol.* 2015;49(8):803-809. https://doi.org/10.1016/j.alcohol.2015.04.005.
46. Shurman J, Koob GF, Gutstein HB. Opioids, pain, the brain, and hyperkatifeia: A framework for the rational use of opioids for pain. *Pain Med.* 2010;11(7):1092-1098. https://doi.org/10.1111/j.1526-4637.2010.00881.x.
47. Pahng AR, Edwards S. Measuring pain avoidance-like behavior in drug-dependent rats. *Curr Protoc Neurosci.* 2018;85(1):e53. https://doi.org/10.1002/cpns.53.
48. Tappe-Theodor A, King T, Morgan MM. Pros and cons of clinically relevant methods to assess pain in rodents. *Neurosci Biobehav Rev.* 2019;100:335-343. https://doi.org/10.1016/j.neubiorev.2019.03.009.
49. Pahng AR, Paulsen RI, McGinn MA, Edwards KN, Edwards S. Neurobiological correlates of pain avoidance-like behavior in morphine-dependent and non-dependent rats. *Neuroscience.* 2017;366:1-14. https://doi.org/10.1016/j.neuroscience.2017.09.055.
50. Harte SE, Meyers JB, Donahue RR, Taylor BK, Morrow TJ. Mechanical conflict system: A novel operant method for the assessment of nociceptive behavior. *PLoS One.* 2016;11(2):e0150164. https://doi.org/10.1371/journal.pone.0150164.
51. Anderson EM, Mills R, Nolan TA, et al. Use of the Operant Orofacial Pain Assessment Device (OPAD) to measure changes in nociceptive behavior. *J Vis Exp.* 2013;(76):e50336. https://doi.org/10.3791/50336.
52. Vendruscolo LF, Schlosburg JE, Misra KK, Chen SA, Greenwell TN, Koob GF. Escalation patterns of varying periods of heroin access. *Pharmacol Biochem Behav.* 2011;98(4):570-574. https://doi.org/10.1016/j.pbb.2011.03.004.
53. Wade CL, Vendruscolo LF, Schlosburg JE, Hernandez DO, Koob GF. Compulsive-like responding for opioid analgesics in rats with extended access. *Neuropsychopharmacology.* 2015;40(2):421-428. https://doi.org/10.1038/npp.2014.188.
54. Edwards S, Vendruscolo LF, Schlosburg JE, et al. Development of mechanical hypersensitivity in rats during heroin and ethanol dependence: Alleviation by CRF_1 receptor antagonism. *Neuropharmacology.* 2012;62(2):1142-1151. https://doi.org/10.1016/j.neuropharm.2011.11.006.
55. Gilpin NW, Richardson HN, Cole M, Koob GF. Vapor inhalation of alcohol in rats. *Curr Protoc Neurosci.* 2008;Chapter 9:Unit 9.29. https://doi.org/10.1002/0471142301.ns0929s44.
56. Roltsch Hellard EA, Impastato RA, Gilpin NW. Intra-cerebral and intra-nasal melanocortin-4 receptor antagonist blocks withdrawal hyperalgesia in alcohol-dependent rats. *Addict Biol.* 2017;22(3):692-701. https://doi.org/10.1111/adb.12360.
57. de Guglielmo G, Kallupi M, Cole MD, George O. Voluntary induction and maintenance of alcohol dependence in rats using alcohol vapor self-administration. *Psychopharmacology (Berl).* 2017;234(13):2009-2018. https://doi.org/10.1007/s00213-017-4608-7.
58. Dina OA, Barletta J, Chen X, et al. Key role for the epsilon isoform of protein kinase C in painful alcoholic neuropathy in the rat. *J Neurosci.* 2000;20(22):8614-8619. https://doi.org/10.1523/jneurosci.20-22-08614.2000.

59. Fu R, Gregor D, Peng Z, Li J, Bekker A, Ye J. Chronic intermittent voluntary alcohol drinking induces hyperalgesia in Sprague-Dawley rats. *Int J Physiol Pathophysiol Pharmacol.* 2015;7(3):136-144.
60. Bergeson SE, Blanton H, Martinez JM, et al. Binge ethanol consumption increases inflammatory pain responses and mechanical and cold sensitivity: Tigecycline treatment efficacy shows sex differences. *Alcohol Clin Exp Res.* 2016;40(12):2506-2515. https://doi.org/10.1111/acer.13252.
61. Martin TJ, Buechler NL, Kim SA, Ewan EE, Xiao R, Childers SR. Involvement of the lateral amygdala in the antiallodynic and reinforcing effects of heroin in rats after peripheral nerve injury. *Anesthesiology.* 2011;114(3):633-642. https://doi.org/10.1097/ALN.0b013e318209aba7.
62. Zhang Z, Tao W, Hou YY, Wang W, Lu YG, Pan ZZ. Persistent pain facilitates response to morphine reward by downregulation of central amygdala GABAergic function. *Neuropsychopharmacology.* 2014;39(9):2263-2271. https://doi.org/10.1038/npp.2014.77.
63. Hipolito L, Wilson-Poe A, Campos-Jurado Y, et al. Inflammatory pain promotes increased opioid self-administration: Role of dysregulated ventral tegmental area μ opioid receptors. *J Neurosci.* 2015;35(35):12217-12231. https://doi.org/10.1523/JNEUROSCI.1053-15.2015.
64. Robins MT, Heinricher MM, Ryabinin AE. From pleasure to pain, and back again: The intricate relationship between alcohol and nociception. *Alcohol Alcohol.* 2019;54(6):625-638. https://doi.org/10.1093/alcalc/agz067.
65. González-Sepúlveda M, Pozo OJ, Marcos J, Valverde O. Chronic pain causes a persistent anxiety state leading to increased ethanol intake in CD1 mice. *J Psychopharmacol.* 2016;30(2):188-203. https://doi.org/10.1177/0269881115622238.
66. Butler RK, Knapp DJ, Ulici V, Longobardi L, Loeser RF, Breese GR. A mouse model for chronic pain-induced increase in ethanol consumption. *Pain.* 2017;158(3):457-462. https://doi.org/10.1097/j.pain.0000000000000780.
67. Yu W, Hwa LS, Makhijani VH, Besheer J, Kash TL. Chronic inflammatory pain drives alcohol drinking in a sex-dependent manner for C57BL/6J mice. *Alcohol.* 2019;77:135-145. https://doi.org/10.1016/j.alcohol.2018.10.002.
68. McGinn MA, Edwards KN, Edwards S. Chronic inflammatory pain alters alcohol-regulated frontocortical signaling and associations between alcohol drinking and thermal sensitivity. *Neurobiol Pain.* 2020;8:100052. https://doi.org/10.1016/j.ynpai.2020.100052.
69. Porreca F, Navratilova E. Reward, motivation, and emotion of pain and its relief. *Pain.* 2017;158(suppl 1):S43-S49. https://doi.org/10.1097/j.pain.0000000000000798.
70. Cahill CM, Walwyn W, Taylor AMW, Pradhan AAA, Evans CJ. Allostatic mechanisms of opioid tolerance beyond desensitization and downregulation. *Trends Pharmacol Sci.* 2016;37(11):963-976. https://doi.org/10.1016/j.tips.2016.08.002.
71. Vogt BA. Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci.* 2005;6(7):533-544. https://doi.org/10.1038/nrn1704.
72. Ploghaus A, Tracey I, Gati JS, et al. Dissociating pain from its anticipation in the human brain. *Science.* 1999;284(5422):1979-1981. https://doi.org/10.1126/science.284.5422.1979.
73. Casey KL, Svensson P, Morrow TJ, Raz J, Jone C, Minoshima S. Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol.* 2000;84(1):525-533. https://doi.org/10.1152/jn.2000.84.1.525.
74. Fuchs PN, Peng YB, Boyette-Davis JA, Uhelski ML. The anterior cingulate cortex and pain processing. *Front Integr Neurosci.* 2014;8:35. https://doi.org/10.3389/fnint.2014.00035.
75. Xiao X, Zhang YQ. A new perspective on the anterior cingulate cortex and affective pain. *Neurosci Biobehav Rev.* 2018;90:200-211. https://doi.org/10.1016/j.neubiorev.2018.03.022.
76. Lu C, Yang T, Zhao H, et al. Insular cortex is critical for the perception, modulation, and chronification of pain. *Neurosci Bull.* 2016;32(2):191-201. https://doi.org/10.1007/s12264-016-0016-y.
77. Moraga-Amaro R, Stehberg J. The insular cortex and the amygdala: Shared functions and interactions. In Ferry B, ed. *The Amygdala–A Discrete Multitasking Manager.* 2012. https://doi.org/10.5772/48495.
78. Menon V, Uddin LQ. Saliency, switching, attention and control: A network model of insula function. *Brain Struct Funct.* 2010;214(5-6):655-667. https://doi.org/10.1007/s00429-010-0262-0.
79. Kim J, Kang I, Chung YA, et al. Altered attentional control over the salience network in complex regional pain syndrome. *Sci Rep.* 2018;8(1):7466. https://doi.org/10.1038/s41598-018-25757-2.
80. Tsai PJ, Keeley RJ, Carmack SA, et al. Converging structural and functional evidence for a rat salience network. *Biol Psychiatry.* 2020;88(11):867-878. https://doi.org/10.1016/j.biopsych.2020.06.023.
81. Zhu X, Sundby K, Bjork JM, Momenan R. Alcohol dependence and altered engagement of brain networks in risky decisions. *Front Hum Neurosci.* 2016;10:142. https://doi.org/10.3389/fnhum.2016.00142.
82. Seo D, Lacadie CM, Sinha R. Neural correlates and connectivity underlying stress-related impulse control difficulties in alcoholism. *Alcohol Clin Exp Res.* 2016;40(9):1884-1894. https://doi.org/10.1111/acer.13166.
83. Jakubczyk A, Wisniewski P, Trucco EM, et al. The synergistic effect between interoceptive accuracy and alcohol use disorder status on pain sensitivity. *Addict Behav.* 2021;112:106607. https://doi.org/10.1016/j.addbeh.2020.106607.
84. Rocchi G, Sterlini B, Tardito S, et al. Opioidergic system and functional architecture of intrinsic brain activity: Implications for psychiatric disorders. *Neuroscientist.* 2020;26(4):343-358. https://doi.org/10.1177/1073858420902360.
85. Ma N, Liu Y, Li N, et al. Addiction related alteration in resting-state brain connectivity. *Neuroimage.* 2010;49(1):738-744. https://doi.org/10.1016/j.neuroimage.2009.08.037.
86. Li Q, Liu J, Wang W, et al. Disrupted coupling of large-scale networks is associated with relapse behaviour in heroin-dependent men. *J Psychiatry Neurosci.* 2018;43(1):48-57. https://doi.org/10.1503/jpn.170011.
87. Smith ML, Walcott AT, Heinricher MM, Ryabinin AE. Anterior cingulate cortex contributes to alcohol withdrawal-induced and socially transferred hyperalgesia. *eNeuro.* 2017;4(4):ENEURO.0087-17.2017. https://doi.org/10.1523/ENEURO.0087-17.2017.
88. O'Sullivan SJ, Schwaber JS. Similarities in alcohol and opioid withdrawal syndromes suggest common negative reinforcement mechanisms involving the interoceptive antireward pathway. *Neurosci Biobehav Rev.* 2021;125:355-364. https://doi.org/10.1016/j.neubiorev.2021.02.033.
89. McGinn MA, Pantazis CB, Tunstall BJ, et al. Drug addiction co-morbidity with alcohol: Neurobiological insights. *Int Rev Neurobiol.* 2021;157:409-472. https://doi.org/10.1016/bs.irn.2020.11.002.
90. Edwards S, Little HJ, Richardson HN, Vendruscolo LF. Divergent regulation of distinct glucocorticoid systems in alcohol dependence. *Alcohol.* 2015;49(8):811-816. https://doi.org/10.1016/j.alcohol.2015.04.004.
91. Vendruscolo LF, Barbier E, Schlosburg JE, et al. Corticosteroid-dependent plasticity mediates compulsive alcohol drinking in rats. *J Neurosci.* 2012;32(22):7563-7571. https://doi.org/10.1523/JNEUROSCI.0069-12.2012.

92. Vendruscolo LF, Estey D, Goodell V, et al. Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals. *J Clin Invest.* 2015;125(8):3193-3197. https://www.jci.org/articles/view/79828.
93. Dina OA, Khasar SG, Alessandri-Haber N, Green PG, Messing RO, Levine JD. Alcohol-induced stress in painful alcoholic neuropathy. *Eur J Neurosci.* 2008;27(1):83-92. https://doi.org/10.1111/j.1460-9568.2007.05987.x.
94. Evans CJ, Cahill CM. Neurobiology of opioid dependence in creating addiction vulnerability. *F1000Res.* 2016;5(F1000 Faculty Rev):1748. https://doi.org/10.12688/f1000research.8369.1.
95. Koob GF. Neurobiology of opioid addiction: Opponent process, hyperkatifeia, and negative reinforcement. *Biol Psychiatry.* 2020;87(1):44-53. https://doi.org/10.1016/j.biopsych.2019.05.023.
96. Bearn J, Buntwal N, Papadopoulos A, Checkley S. Salivary cortisol during opiate dependence and withdrawal. *Addict Biol.* 2001;6(2):157-162. https://doi.org/10.1080/13556210020040235.
97. Carmack SA, Keeley RJ, Vendruscolo JCM, et al. Heroin addiction engages negative emotional learning brain circuits in rats. *J Clin Invest.* 2019;129(6):2480-2484. https://doi.org/10.1172/JCI125534.
98. Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: A psychoneuroendocrine rationale for stress management in pain rehabilitation. *Phys Ther.* 2014;94(12):1816-1825. https://doi.org/10.2522/ptj.20130597.

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Forebrain-Midbrain Circuits and Peptides Involved in Hyperalgesia After Chronic Alcohol Exposure

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People living with pain report drinking alcohol to relieve pain. Acute alcohol use reduces pain, and chronic alcohol use facilitates the emergence or exaggeration of pain. Recently, funding agencies and neuroscientists involved in basic research have turned their attention to understanding the neurobiological mechanisms that underlie pain-alcohol interactions, with a focus on circuit and molecular mediators of alcohol-induced changes in pain-related behavior. This review briefly discusses some examples of work being done in this area, with a focus on reciprocal projections between the midbrain and extended amygdala, as well as some neurochemical mediators of pain-related phenotypes after alcohol exposure. Finally, as more work accumulates on this topic, the authors highlight the need for the neuroscience field to carefully consider sex and age in the design and analysis of pain-alcohol interaction experiments.

KEYWORDS: alcohol; pain; withdrawal; dependence; hyperalgesia; allodynia

Chronic pain increases the risk for development of alcohol use disorder (AUD). Given that acute alcohol consumption can reduce pain, humans sometimes drink alcohol for relief of pain. Chronic alcohol consumption, however, can increase pain sensitivity during withdrawal and facilitate pain sensitization related to comorbid pain conditions.[1] Ascending and descending nociceptive circuitry

and higher order pain processing centers exhibit a high degree of overlap with the brain circuits that mediate behaviors associated with alcohol reinforcement and with AUD, alcohol dependence and withdrawal.[1] Recently, the National Institute on Alcohol Abuse and Alcoholism has prioritized research that aims to uncover the neurobiological mechanisms that underlie pain-associated increases in alcohol drinking (i.e., self-medication) and the emergence or exaggeration of pain phenotypes by chronic alcohol exposure. Layered into this research topic are questions of sex differences and species differences, age at time of alcohol exposure and testing, and potential effects of dose, duration, route, and pattern of alcohol exposure. In response to this programmatic shift, neuroscientists involved in basic research have increased their investigation of the neurobiological mechanisms underlying these phenomena, including circuit interrogation and testing the role of neuropeptides, which are the two focal points of this review. Discussed below are the roles of two circuits between the limbic forebrain and the midbrain, more specifically, projections descending from the central amygdala (CeA) to the periaqueductal gray (PAG) and projections ascending from the PAG to the bed nucleus of the stria terminalis (BNST), as well as peptidergic transmission within those regions and circuits, in mediating alcohol-pain interactions. Although each of these brain regions can be subdivided, the literature in this area is in its nascent stages and in many cases the contributions of subregions have not been examined; therefore, this review's language regarding brain regions reflects the resolution provided within the cited studies.

SUPRASPINAL CIRCUITS IN ALCOHOL WITHDRAWAL HYPERALGESIA

In the brain, the molecular and cellular mechanisms involved in pain processing are complex and diverse. The ventrolateral PAG (vlPAG) receives information from ascending pain pathways and is a major source of descending outputs responsible for inhibitory control of pain.[2,3] In adult male and female Sprague-Dawley rats, the analgesic and antihyperalgesic effects of opioid receptor agonists are in part attributed to their action in the PAG.[4] More specifically, opioid drugs can reduce pain in adult male Sprague-Dawley rats by facilitating the activity of descending vlPAG outputs to the rostral ventrolateral medulla (RVM),[5,6] and evidence suggests that endogenous opioids may modulate pain similarly in rodents.[7] In adolescent male Swiss Webster mice, mu opioid receptor activation also disinhibits tyrosine hydroxylase (TH)-positive (i.e., dopaminergic [DAergic]) neurons in the PAG via local gamma-aminobutyric acid-ergic (GABAergic) inputs.[8] Therefore, the PAG receives input from ascending pain modulation pathways, has reciprocal connections with the limbic forebrain, and mediates the analgesic effects of opioid drugs via multiple mechanisms and circuits. Furthermore, chronic alcohol exposure produces plasticity in the CeA[9] and BNST,[10] both of which are inputs to the PAG,[11,12] suggesting that the same circuitry responsible for pain modulation may be sensitive to prolonged alcohol use.

A majority of prior work examining the neurobiology of alcohol has focused on the investigation of individual brain regions, but progressively more attention is being paid to the acute and chronic effects of alcohol on brain circuits involved in nociception. The ultimate goal of circuit-level analysis of alcohol-related hyperalgesia is to facilitate the identification of potential treatment targets in humans with AUD living with pain. This may be achieved by establishing the molecular signature of cells that modulate pain and nociception via projections to other brain regions. For example, if specific receptor subtypes are preferentially enriched on a subset of projection neurons, then pharmacological modulation of those receptors may present a unique opportunity to modulate that circuit for reducing pain-related outcomes with minimal off-target effects.

VLPAG/DR TO BNST: AN ASCENDING ANTINOCICEPTIVE CIRCUIT

Dopamine (DA) neurons in the vlPAG/dorsal raphe (DR) were first characterized in a series of neuroanatomical studies, where they were reported to be a dorso-caudal extension of the ventral tegmental area (VTA).[13,14] Dopamine neurons in the vlPAG/DR are disinhibited by mu opioid receptor agonists and have roles in mediating pain and arousal in rats and mice of various strains and ages.[8,14–22] Notably, the vlPAG/DR and VTA project to the extended amygdala, where co-release of DA and glutamate activates neurons in the BNST and the CeA of rats and mice.[8,23-24] Therefore, it is reasonable to postulate that DA signaling in these extended-amygdala structures alters some aspects of the pain experience.

In support of this notion, bath application of alcohol promotes firing of vlPAG/DR DA neurons in brain slices taken from adolescent male Swiss Webster mice, potentially via modulation of glutamatergic transmission.[25] Furthermore, systemic administration via intraperitoneal injection of alcohol or morphine can increase extracellular DA levels in the BNST of presumably adult (230–250 g) male Sprague-Dawley rats,[26] and morphine increases phosphorylation of extracellular signal–regulated kinase (ERK) via dopamine D1 receptors in adult male and female C57 mice,[27] suggesting that drugs of misuse may modulate pain via activation of DA inputs to the BNST. Given the role of the BNST in regulating emotional and motivational behaviors, vlPAG/DR DAergic projections to the BNST may mediate or mitigate the affective aspects of chronic pain. Interestingly, both chemogenetic activation of vlPAG/DR DAergic neurons and optogenetic activation of vlPAG/DR TH-positive outputs to the BNST are antinociceptive in adolescent[8] and adult[20,28] male mice. This antinociceptive effect manifests as a reduction in basal pain sensitivity and attenuation of hypersensitivity after persistent intraplantar inflammation, demonstrating a possible role for DAergic projections from the vlPAG/DR to the BNST in pain-related outcomes.

THE VLPAG/DR-BNST CIRCUIT IN SEX-SPECIFIC MECHANISMS OF PAIN

In humans, pain drives greater functional connectivity between the PAG and limbic structures in men relative to women,[29] but the mechanisms behind these differences are unclear. Only a few molecular drivers of sex differences have been identified for pain,[30] with some evidence supporting a role for DA signaling in the vlPAG/DR and the BNST. In the midbrain, the vlPAG-RVM circuit is critical for mediating morphine antinociception and tolerance to this effect in adult male Sprague-Dawley rats;[4] the same effects are facilitated, at least in part, by morphine-microglia interactions in adult female Sprague-Dawley rats.[31] Chronic inflammatory pain increases presynaptic GABA release but decreases high-affinity tonic gamma-aminobutyric acid type A ($GABA_A$) receptor-mediated currents exclusively in vlPAG neurons of adolescent female Sprague-Dawley rats, an effect that may be associated with sex-specific morphine-induced antinociception, which was measured in adult Sprague-Dawley rats in the same study.[32] These data suggest that opioids and chronic inflammation alter GABAergic signaling in the vlPAG and influence pain sensitivity differently for males and females. Considering that the same vlPAG GABAergic neurons that regulate the activity of RVM-projecting cells also may govern the activity of vlPAG DAergic neurons in adolescent and adult mice,[8,22] it is possible that BNST-projecting vlPAG/DR DA-positive cells contribute to sex differences in pain processing. Previous work from the Kash lab and others have shown that DAergic cells in the vlPAG/DR robustly project to the BNST and that their activation reduces pain-related behaviors in adolescent and adult male

mice,[8,20] but these evaluations were performed only in male mice and did not examine circuit activity. Newly published data from the Kash lab indicate that optogenetic activation of DAergic inputs from the vlPAG/DR to the BNST alters nociception in adult male but not female C57 mice,[28] and that this activation is associated with subtle changes in dopamine receptor function assessed in brain slices. In contrast, local antagonism of DA D1 receptor in the BNST increases pain-like behavior only in adult female rats.[33] These data suggest not only sex differences, but also species differences, in the role of DAergic inputs from the vlPAG/DR to the BNST in mediating pain-related behavior.

DA REGULATION OF CRF FUNCTION IN THE BNST, SEX, AND REGULATION OF PAIN

The BNST is a center of integration for value representation, motivated behaviors, threat response, and drug use.[34] Although the potential role of the BNST in pain is not well characterized, it has been suggested that corticotropin-releasing factor (CRF) signaling in the BNST has a role in the sensory and affective-motivational components of pain,[35-41] which parallels data showing that CRF signaling in the CeA of adult male Sprague-Dawley rats facilitates pain-like responses via actions at CRF type-1 receptor (CRFR1).[42] Evidence for DA-CRF interactions comes from findings that DA enhancement of glutamatergic synaptic transmission in the BNST is regulated by CRFR1 activity in adolescent male C57 mice.[43] Although it has been assumed that this DA comes from the VTA, the vlPAG/DR remains an intriguing possibility as the source of DA in the BNST. Because DA neurons in the vlPAG/DR co-express vasoactive intestinal peptide (VIP) in mice[44] and VIP neurons in the vlPAG/DR terminate onto CRF neurons in the BNST, vlPAG/DR DA neurons may directly influence CRF signaling by innervating CRF neurons in the BNST. A more direct indication by Meloni et al. (2006)[45] shows that in adult male Sprague-Dawley rats, the majority of DA neurons innervating CRF neurons in the BNST originate in the vlPAG/DR. Therefore, vlPAG/DR DA neurons may interact with CRF signaling via direct cellular transmission onto CRF neurons in the BNST. Finally, BNST anatomy, CRF distribution,[46] DA modulation of pain[33] and behavioral effects[47] differ in male and female rats and mice. Therefore, it is possible that DA cells in the vlPAG/DR and CRF cells in the BNST work together to contribute to sex differences in pain. The Kash lab has begun to explore this possibility using in vivo imaging.[48] Briefly, the authors found that CRF neurons in the BNST are dynamically engaged during nociceptive processing; however, there is reduced activation of BNST CRF neurons during noxious heat exposure in adult female mice compared to males. It will be critically important to determine if the dynamics of CRF neurons in the BNST are altered following alcohol exposure. Although there has been more focus on the role of dopaminergic innervation of the BNST in pain-related outcomes, one study reported that activation of serotonergic projections from the DR to the CeA reduces negative affective behavior in adult male mice with chronic inflammatory or neuropathic pain.[49] This finding is especially intriguing given that selective serotonin reuptake inhibitors have been used to treat both AUD and pain disorders.

CEA TO VLPAG PROJECTIONS IN ALCOHOL WITHDRAWAL HYPERALGESIA

The vlPAG is densely innervated by descending inputs from the CeA.[50,51] In the context of chronic pain models, the CeA and its projections to the vlPAG have been tested for their role in pain-related behaviors in adult and adolescent rats and mice.[52-56] Early studies showed that electrical stimulation of the CeA in rodents produces analgesia, and that this effect is blocked by lidocaine-induced inactivation of PAG or by opioid receptor blockade in PAG, suggesting that cells

projecting from the CeA to the PAG modulate the nocifensive response in male Wistar rats weighing 140–160 grams.[57] Data from the Gilpin lab show that inactivation of the CeA as a whole (using tetrodotoxin),[58] or inactivation of cells projecting from the CeA to the vlPAG (using optogenetics),[11] is pronociceptive in adult male Wistar rats. Work from other groups shows that ERK activation in the amygdala (manipulations aimed at the CeA) is necessary and sufficient to induce lasting mechanical hypersensitivity in male Swiss Webster mice weighing 40–45 grams.[54] In recent years, it has become increasingly clear that the role of the CeA in mediating pain-like responses is affected by the CeA subregion (medial versus lateral division)[55] and CeA cell type (according to their morphology, electrophysiology and molecular signature)[52] being examined, as well as laterality of pain and amygdala,[53] and possibly also by chronic pain state, species, sex, and age of experimental subjects.

Based on this prior work, the Gilpin lab investigated the relationship between chronic exposure to high-dose alcohol, CeA-vlPAG circuit activity, and pain-related outcomes in rats. Adult male Wistar rats rendered alcohol-dependent via long-term alcohol vapor exposure (i.e., exposure models that produce physiological and behavioral signs of withdrawal upon termination of alcohol exposure) exhibit thermal hyperalgesia during withdrawal, which is not observed in rats that are nondependent alcohol drinkers or alcohol-naïve controls.[59] This effect is reversed by acute bolus systemic alcohol injections and by oral alcohol self-administration prior to nociception testing.[59] In subsequent work using optogenetic stimulation of CeA terminals in the vlPAG, alcohol-dependent adult male Wistar rats exhibited weaker connectivity between the CeA and the vlPAG during alcohol withdrawal, as evidenced by lower amplitude of inhibitory postsynaptic currents.[11] The authors also showed that pro-nociceptive manipulations in the CeA of rats can be reversed by mu opioid receptor blockade in the vlPAG (confirming the result found by Oliveira and Prado in 2001,[57] mentioned above), that optogenetic activation of CeA neurons projecting to the vlPAG attenuates hyperalgesia associated with alcohol withdrawal in alcohol-dependent rats, and that inhibition of these neurons produces thermal hyperalgesia in otherwise experimentally naïve adult male Wistar rats.[11]

AMYGDALAR MC4R SIGNALING IN ALCOHOL WITHDRAWAL HYPERALGESIA

Chronic alcohol exposure and withdrawal alters melanocortin 4 receptor (MC4R) expression in the CeA of adult male Wistar and Sprague-Dawley rats,[11,60] and site-specific antagonism of MC4Rs in the CeA reverses alcohol withdrawal hyperalgesia in adult male Wistar rats.[11] Antagonism of MC4Rs in the amygdala facilitates the antinociceptive effects of morphine and prevents the development of tolerance to the analgesic effects of morphine as well as the emergence of paradoxical hyperalgesia during morphine withdrawal in adult male Sprague-Dawley and Wistar rats.[61,62] Furthermore, MC4R antagonism reduces neuropathic pain in adult male Wistar rats.[63,64]

MC4Rs are expressed at most levels of the ascending and descending pain circuitry and induce plasticity by altering trafficking of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to the membrane.[65] Therefore, it would be of interest to know whether MC4R expression is enriched specifically in cells linking brain regions important for pain processing, that is, in pain circuits (e.g., on the postsynaptic membranes of vlPAG-projecting cells in the CeA). It is unclear whether MC4Rs are expressed or enriched on the postsynaptic membrane of vlPAG-projecting cells in the CeA. Ongoing work is examining whether this is the case and aims to test whether modulation of MC4R activity on vlPAG-projecting CeA cells attenuates alcohol withdrawal hyperalgesia and other pain states. Collectively, there is growing literature showing that MC4R antagonism in the CeA—and other sites in the central nervous system—reduces pain-related behavior in multiple

pain states. This is exciting when one considers that intranasal delivery of an MC4R antagonist blocks alcohol withdrawal hyperalgesia in adult male Wistar rats[59] and reduces anxiety-like behavior in male Sprague-Dawley rats weighing 150–160 grams,[66] suggesting that intranasal delivery of MC4R antagonists to treat pain conditions may hold promise for translation to the clinic.

AMYGDALAR CRF SIGNALING IN ALCOHOL WITHDRAWAL HYPERALGESIA

Many years of research have been devoted to understanding the behavioral effects of CRF-CRFR1 signaling in the CeA. Much of this work has focused on addiction-related behaviors, anxiety-like behavior, stress reactivity, fear-related behavior, and nociception in rats and mice.[9,56,67] CRF and CRFR1 messenger RNA (mRNA) and protein levels are highly expressed in the CeA of adult male Wistar rats,[68] CRF increases inhibitory transmission in the CeA, and this effect is altered by alcohol dependence in adolescent male Sprague-Dawley rats.[69] In the same study, chronic in vivo systemic CRFR1 antagonism during alcohol withdrawal prevented the emergence of dependence-like phenotypes during subsequent withdrawals in adult male Wistar rats.[69] Antagonism of CRFR1 in the CeA acutely reduces anxiety-like behavior in adult male Wistar rats,[70] reduces avoidant behaviors in adult male Wistar rats with high stress reactivity,[71] reduces escalation of alcohol drinking in alcohol-dependent and stressed adult male Wistar rats,[68,71] and attenuates hyperalgesia induced by nicotine dependence and predator odor stress in adult male Wistar rats.[58,72]

Recent work from the Gilpin lab shows that chronic alcohol exposure during adolescence leads to hyperalgesia and reductions in synaptic drive onto vlPAG-projecting CeA cells in rats, effects that last many weeks after termination of alcohol exposure in male but not female Wistar rats.[73] This latter finding is in agreement with prior work from the authors showing weaker CeA-vlPAG connectivity in alcohol-dependent adult male Wistar rats that are hyperalgesic during acute withdrawal.[11] It remains to be determined whether the effects of CRFR1 in the CeA on alcohol withdrawal hyperalgesia can be attributed to their expression on specific subsets of CeA projection cells. Ongoing work by the authors seeks to build on these initial circuit-level findings by determining (1) how the CeA-vlPAG circuit is modulated by the activity of specific peptide systems during alcohol withdrawal, and (2) the role of these cell type-specific circuits in mediating alcohol withdrawal hyperalgesia.

BIOLOGICAL FACTORS IN ALCOHOL WITHDRAWAL HYPERALGESIA

Men and women experience, process, and report pain differently.[74,75] Similarly, rodents exhibit sex differences in baseline nociception and responses to the antinociceptive effects of analgesic drugs.[76] Under healthy and chronic pain conditions, humans and non-human animals exhibit diffuse noxious inhibitory control (DNIC) of pain (also called inhibition of pain by pain) that is modulated by sex.[77,78] In rats, DNIC is less efficient in females compared with males, and the brain networks engaged during DNIC differ in males and females.[77] The above discussion of sex differences in pain modulation by vlPAG/DR circuit projections to the BNST is a good example of why it is critical for the nascent alcohol-pain field to include both sexes in all studies.

It is largely unknown how the age of onset for chronic pain affects (1) pain-induced alterations in the central nervous system, (2) neurobiological mediators of the effects of pain on behavior, and (3) the modality, intensity, and duration of chronic pain–related behavior. For example, in the CeA, some studies of chronic inflammatory pain have been performed in adult mice,[52] and others have been performed in adolescent mice.[55] In those studies, CeA cells were sorted and

classified according to firing pattern (e.g., regular spiking, fast spiking, late firing, bursting), and the resulting cell population breakdown differed greatly between the two studies. Thus, even when measuring similar physiological outcomes in vitro in the CeA of mice treated with the same in vivo manipulation (i.e., CFA to induce chronic inflammatory pain), results may vary. There are several possible explanations for these discrepant results, but one potential major contributor to these results is the age of rodents at the time of CFA treatment and sacrifice. In the context of pain-alcohol relationships, age may be especially important because (1) alcohol effects on the central nervous system differ according to age of exposure, and (2) human data show that the relationship between pain severity and alcohol use begins early in life, and that childhood trauma is associated with increased risk of chronic pain in adulthood.[79,80] As mentioned above, chronic alcohol exposure during adolescence produces mechanical hypersensitivity and thermal hyperalgesia that last for many weeks following termination of alcohol exposure, but the underlying neurobiological mediators of these effects are unknown. As more research is devoted to testing the neurobiological mechanisms underlying pain-alcohol interactions, it will be important for the field to pay close attention to sex and age differences.

CONCLUSIONS

Neuroscience has recently turned its attention to understanding the neurobiological mechanisms that underlie pain-alcohol interactions. This new research has primarily focused on the emergence of pain-like states after chronic alcohol exposure using animal models, but it also should focus on alcohol use and alcohol effects in rodents with chronic inflammatory or neuropathic pain. To this point, work has focused largely on circuit and molecular mediators of alcohol-related hyperalgesia. Above, this review discusses examples of recent work in this area, with a focus on reciprocal projections between midbrain and the limbic forebrain (i.e., extended amygdala) as well as some neurochemical mediators (dopamine, melanocortins, and CRF) of pain-related phenotypes after alcohol exposure. This list undoubtedly will grow as more labs begin to work in this area, and it will be important going forward for the field to be mindful of sex and age (as well as species) in study design and data analysis of pain-alcohol interactions.

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References

1. Egli M, Koob GF, Edwards S. Alcohol dependence as a chronic pain disorder. *Neurosci Biobehav Rev.* 2012;36(10):2179-2192. https://doi.org/10.1016/j.neubiorev.2012.07.010.
2. Millan MJ. Descending control of pain. *Prog Neurobiol.* 2002;66(6):355-474. https://doi.org/10.1016/s0301-0082(02)00009-6.
3. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron.* 2007;55(3):377-391. https://doi.org/10.1016/j.neuron.2007.07.012.
4. Loyd DR, Morgan MM, Murphy AZ. Morphine preferentially activates the periaqueductal gray-rostral ventromedial medullary pathway in the male rat: A potential mechanism for sex differences in antinociception. *Neuroscience.* 2007;147(2):456-468. https://doi.org/10.1016/j.neuroscience.2007.03.053.
5. Basbaum AI, Fields HL. Endogenous pain control systems: Brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci.* 1984;7:309-338. https://doi.org/10.1146/annurev.ne.07.030184.001521.

6. Hirakawa N, Tershner SA, Fields HL. Highly delta selective antagonists in the RVM attenuate the antinociceptive effect of PAG DAMGO. *Neuroreport.* 1999;10(15):3125-3129. https://doi.org/10.1097/00001756-199910190-00001.
7. Bagley EE, Ingram SL. Endogenous opioid peptides in the descending pain modulatory circuit. *Neuropharmacology.* 2020;173:108131. https://doi.org/10.1016/j.neuropharm.2020.108131.
8. Li C, Sugam JA, Lowery-Gionta EG, et al. Mu opioid receptor modulation of dopamine neurons in the periaqueductal gray/dorsal raphe: A role in regulation of pain. *Neuropsychopharmacology.* 2016;41(8):2122-2132. https://doi.org/10.1038/npp.2016.12.
9. Gilpin NW, Herman MA, Roberto M. The central amygdala as an integrative hub for anxiety and alcohol use disorders. *Biol Psychiatry.* 2015;77(10):859-869. https://doi.org/10.1016/j.biopsych.2014.09.008.
10. Vranjkovic O, Pina M, Kash TL, Winder DG. The bed nucleus of the stria terminalis in drug-associated behavior and affect: A circuit-based perspective. *Neuropharmacology.* 2017;122:100-106. https://doi.org/10.1016/j.neuropharm.2017.03.028.
11. Avegno EM, Lobell TD, Itoga CA, et al. Central amygdala circuits mediate hyperalgesia in alcohol-dependent rats. *J Neurosci.* 2018;38(36):7761-7773. https://doi.org/10.1523/jneurosci.0483-18.2018.
12. Siciliano CA, Noamany H, Chang CJ, et al. A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. *Science.* 2019;366(6468):1008-1012. https://doi.org/10.1126/science.aay1186.
13. Hökfelt T, Quiron R, Bjorklund A. Distribution of tyrosine-hydroxylase immunoreactive neurons in the rat brain. 1984.
14. Lu J, Jhou TC, Saper CB. Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. *J Neurosci.* 2006;26(1):193-202. https://doi.org/10.1523/jneurosci.2244-05.2006.
15. Flores JA, El Banoua F, Galán-Rodríguez B, Fernandez-Espejo E. Opiate anti-nociception is attenuated following lesion of large dopamine neurons of the periaqueductal grey: Critical role for D1 (not D2) dopamine receptors. *Pain.* 2004;110(1-2):205-214. https://doi.org/10.1016/j.pain.2004.03.036.
16. Flores JA, Galán-Rodríguez B, Ramiro-Fuentes S, Fernandez-Espejo E. Role for dopamine neurons of the rostral linear nucleus and periaqueductal gray in the rewarding and sensitizing properties of heroin. *Neuropsychopharmacology.* 2006;31(7):1475-1488. https://doi.org/10.1038/sj.npp.1300946.
17. Matthews GA, Nieh EH, Vander Weele CM, et al. Dorsal raphe dopamine neurons represent the experience of social isolation. *Cell.* 2016;164(4):617-631. https://doi.org/10.1016/j.cell.2015.12.040.
18. Cho JR, Treweek JB, Robinson JE, et al. Dorsal raphe dopamine neurons modulate arousal and promote wakefulness by salient stimuli. *Neuron.* 2017;94(6):1205-1219.e8. https://doi.org/10.1016/j.neuron.2017.05.020.
19. Groessl F, Munsch T, Meis S, et al. Dorsal tegmental dopamine neurons gate associative learning of fear. *Nat Neurosci.* 2018;21(7):952-962. https://doi.org/10.1038/s41593-018-0174-5.
20. Taylor NE, Pei J, Zhang J, et al. The role of glutamatergic and dopaminergic neurons in the periaqueductal gray/dorsal raphe: Separating analgesia and anxiety. *eNeuro.* 2019;6(1):ENEURO.0018-18.2019. https://doi.org/10.1523/eneuro.0018-18.2019.
21. Porter-Stransky KA, Centanni SW, Karne SL, et al. Noradrenergic transmission at alpha1-adrenergic receptors in the ventral periaqueductal gray modulates arousal. *Biol Psychiatry.* 2019;85(3):237-247. https://doi.org/10.1016/j.biopsych.2018.07.027.
22. Lin R, Liang J, Wang R, et al. The raphe dopamine system controls the expression of incentive memory. *Neuron.* 2020;106(3):498-514.e8. https://doi.org/10.1016/j.neuron.2020.02.009.
23. Avegno EM, Kasten CR, Snyder WB 3rd, et al. Alcohol dependence activates ventral tegmental area projections to central amygdala in male mice and rats. *Addict Biol.* 2021;26(4):e.12990. https://doi.org/10.1111/adb.12990.
24. Mingote S, Chuhma N, Kusnoor SV, Field B, Deutch AY, Rayport S. Functional connectome analysis of dopamine neuron glutamatergic connections in forebrain regions. *J Neurosci.* 2015;35(49):16259-16271. https://doi.org/10.1523/jneurosci.1674-15.2015.
25. Li C, McCall NM, Lopez AJ, Kash TL. Alcohol effects on synaptic transmission in periaqueductal gray dopamine neurons. *Alcohol.* 2013;47(4):279-287. https://doi.org/10.1016/j.alcohol.2013.02.002.
26. Carboni E, Silvagni A, Rolando MT, Di Chiara G. Stimulation of in vivo dopamine transmission in the bed nucleus of stria terminalis by reinforcing drugs. *J Neurosci.* 2000;20(20):RC102. https://doi.org/10.1523/jneurosci.20-20-j0002.2000.
27. Valjent E, Pascoli V, Svenningsson P, et al. Regulation of a protein phosphatase cascade allows convergent dopamine and glutamate signals to activate ERK in the striatum. *Proc Natl Acad Sci U S A.* 2005;102(2):491-496. https://doi.org/10.1073/pnas.0408305102.
28. Yu W, Pati D, Pina MM, et al. Periaqueductal gray/dorsal raphe dopamine neurons contribute to sex differences in pain-related behaviors. *Neuron.* 2021;109(8):1365-1380.e5. https://doi.org/10.1016/j.neuron.2021.03.001.
29. Linnman C, Beucke JC, Jensen KB, Gollub RL, Kong J. Sex similarities and differences in pain-related periaqueductal gray connectivity. *Pain.* 2012;153(2):444-454. https://doi.org/10.1016/j.pain.2011.11.006.
30. Mogil JS. Qualitative sex differences in pain processing: Emerging evidence of a biased literature. *Nat Rev Neurosci*. 2020;21(7):353-365. https://doi.org/10.1038/s41583-020-0310-6.
31. Doyle HH, Eidson LN, Sinkiewicz DM, Murphy AZ. Sex differences in microglia activity within the periaqueductal gray of the rat: A potential mechanism driving the dimorphic effects of morphine. *J Neurosci.* 2017;37(12):3202–3214. https://doi.org/10.1523/jneurosci.2906-16.2017.
32. Tonsfeldt KJ, Suchland KL, Beeson KA, Lowe JD, Li MH, Ingram SL. Sex differences in $GABA_A$ signaling in the periaqueductal gray induced by persistent inflammation. *J Neurosci.* 2016;36(5):1669-1681. https://doi.org/10.1523/jneurosci.1928-15.2016.
33. Hagiwara H, Funabashi T, Akema T, Kimura F. Sex-specific differences in pain response by dopamine in the bed nucleus of the stria terminalis in rats. *Neuroreport.* 2013;24(4):181-185. https://doi.org/10.1097/wnr.0b013e32835d8540.
34. Kash TL, Pleil KE, Marcinkiewcz CA, et al. Neuropeptide regulation of signaling and behavior in the BNST. *Mol Cells.* 2015;38(1):1-13. https://doi.org/10.14348/molcells.2015.2261.
35. Deyama S, Nakagawa T, Kaneko S, Uehara T, Minami M. Involvement of the bed nucleus of the stria terminalis in the negative affective component of visceral and somatic pain in rats. *Behav Brain Res.* 2007;176(2):367-371. https://doi.org/10.1016/j.bbr.2006.10.021.
36. Tran L, Schulkin J, Greenwood-Van Meerveld B. Importance of CRF receptor-mediated mechanisms of the bed nucleus of the stria terminalis in the processing of anxiety and pain. *Neuropsychopharmacology.* 2014;39(11):2633-2645. https://doi.org/10.1038/npp.2014.117.

37. Tran L, Wiskur B, Greenwood-Van Meerveld B. The role of the anteriolateral bed nucleus of the stria terminalis in stress-induced nociception. *Am J Physiol Gastrointest Liver Physiol.* 2012;302(11):G1301-G1309. https://doi.org/10.1152/ajpgi.00501.2011.
38. Ide S, Hara T, Ohno A, et al. Opposing roles of corticotropin-releasing factor and neuropeptide Y within the dorsolateral bed nucleus of the stria terminalis in the negative affective component of pain in rats. *J Neurosci.* 2013;33(14):5881-5894. https://doi.org/10.1523/jneurosci.4278-12.2013.
39. Minami M. The role of the bed nucleus of the stria terminalis in pain-induced aversive motivation. *Curr Opin Behav Sci.* 2019;26: 46-53. https://doi.org/10.1016/j.cobeha.2018.10.003.
40. Takahashi D, Asaoka Y, Kimura K, et al. Tonic suppression of the mesolimbic dopaminergic system by enhanced corticotropin-releasing factor signaling within the bed nucleus of the stria terminalis in chronic pain model rats. *J Neurosci.* 2019;39(42): 8376-8385. https://doi.org/10.1523/jneurosci.3047-18.2019.
41. Hara R, Asaoka Y, Takahashi D, Nomura H, Amano T, Minami M. Disappearance of the inhibitory effect of neuropeptide Y within the dorsolateral bed nucleus of the stria terminalis in rats with chronic pain. *Neurosci Lett.* 2020;728:134958. https://doi.org/10.1016/j.neulet.2020.134958.
42. Ji G, Neugebauer V. Pro- and anti-nociceptive effects of corticotropin-releasing factor (CRF) in central amygdala neurons are mediated through different receptors. *J Neurophysiol.* 2008;99(3):1201-1212. https://doi.org/10.1152/jn.01148.2007.
43. Kash TL, Nobis WP, Matthews RT, Winder DG. Dopamine enhances fast excitatory synaptic transmission in the extended amygdala by a CRF-R1-dependent process. *J Neurosci.* 2008;28(51):13856-13865. https://doi.org/10.1523/jneurosci.4715-08.2008.
44. Dougalis AG, Matthews GAC, Bishop MW, Brischouz F, Kobayashi K, Ungless MA. Functional properties of dopamine neurons and co-expression of vasoactive intestinal polypeptide in the dorsal raphe nucleus and ventro-lateral periaqueductal grey. *Eur J Neurosci.* 2012;36(10):3322-3332. https://doi.org/10.1111/j.1460-9568.2012.08255.x
45. Meloni EG, Gerety LP, Knoll AT, Cohen BM, Carlezon WA Jr. Behavioral and anatomical interactions between dopamine and corticotropin-releasing factor in the rat. *J Neurosci.* 2006;26(14):3855-3863. https://doi.org/10.1523/jneurosci.4957-05.2006.
46. Uchida K, Otsuka H, Morishita M, et al. Female-biased sexual dimorphism of corticotropin-releasing factor neurons in the bed nucleus of the stria terminalis. *Biol Sex Diff.* 2019;10(1):6. https://doi.org/10.1186/s13293-019-0221-2.
47. Wiersielis KR, Wicks B, Simko H, et al. Sex differences in corticotropin releasing factor-evoked behavior and activated networks. *Psychoneuroendocrinology.* 2016;73:204-216. https://doi.org/10.1016/j.psyneuen.2016.07.007.
48. Yu W, Caira CM, del R Rivera Sanchez N, Moseley GA, Kash TL. Corticotropin-releasing factor neurons in the bed nucleus of the stria terminalis exhibit sex-specific pain encoding in mice. *Sci Rep.* 2021;11(1):12500. https://doi.org/10.1038/s41598-021-91672-8.
49. Zhou W, Jin Y, Meng Q, et al. A neural circuit for comorbid depressive symptoms in chronic pain. *Nat Neurosci.* 2019;22: 1649-1658. https://doi.org/10.1038/s41593-019-0468-2.
50. Rizvi TA, Ennis M, Behbehani MM, Shipley MT. Connections between the central nucleus of the amygdala and the midbrain periaqueductal gray: Topography and reciprocity. *J Comp Neurol.* 1991;303(1):121-131. https://doi.org/10.1002/cne.903030111.
51. Van Bockstaele EJ, Colago EE, Valentino RJ. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: Substrate for the co-ordination of emotional and cognitive limbs of the stress response. *J Neuroendocrinol.* 1998;10(10):743-757. https://doi.org/10.1046/j.1365-2826.1998.00254.x.
52. Adke AP, Khan A, Ahn HS, et al. Cell-type specificity of neuronal excitability and morphology in the central amygdala. *eNeuro.* 2021;8(1):ENEURO.0402-20.2020. https://doi.org/10.1523/eneuro.0402-20.2020.
53. Allen HN, Bobnar HJ, Kolber BJ. Left and right hemispheric lateralization of the amygdala in pain. *Prog Neurobiol.* 2021; 196:101891. https://doi.org/10.1016/j.pneurobio.2020.101891.
54. Carrasquillo Y, Gereau RW 4th. Activation of the extracellular signal-regulated kinase in the amygdala modulates pain perception. *J Neurosci.* 2007;27(7):1543-1551. https://doi.org/10.1523/jneurosci.3536-06.2007.
55. Li JN, Sheets PL. The central amygdala to periaqueductal gray pathway comprises intrinsically distinct neurons differentially affected in a model of inflammatory pain. *J Physiol.* 2018;596(24):6289-6305. https://doi.org/10.1113/jp276935.
56. Neugebauer V, Mazzitelli M, Cragg B, Ji G, Navratilova E, Porreca F. Amygdala, neuropeptides, and chronic pain-related affective behaviors. *Neuropharmacol.* 2020;170:108052. https://doi.org/10.1016/j.neuropharm.2020.108052.
57. Oliveira MA, Prado WA. Role of PAG in the antinociception evoked from the medial or central amygdala in rats. *Brain Res Bull.* 2001;54(1):55-63. https://doi.org/10.1016/s0361-9230(00)00420-2.
58. Itoga CA, Roltsch Hellard EA, Whitaker AM, et al. Traumatic stress promotes hyperalgesia via corticotropin-releasing factor-1 receptor ($CRFR_1$) signaling in central amygdala. *Neuropsychopharmacology.* 2016;41(10):2463-2472. https://doi.org/10.1038/npp.2016.44.
59. Roltsch Hellard EA, Impastato RA, Gilpin NW. Intra-cerebral and intra-nasal melanocortin-4 receptor antagonist blocks withdrawal hyperalgesia in alcohol-dependent rats. *Addict Biol.* 2017;22(3): 692-701. https://doi.org/10.1111/adb.12360.
60. Navarro M, Cubero I, Knapp DJ, Breese GR, Thiele TE. Decreased immunoreactivity of the melanocortin neuropeptide alpha-melanocyte-stimulating hormone (alpha-MSH) after chronic ethanol exposure in Sprague–Dawley rats. *Alcohol Clin Exp Res.* 2008;32(2):266-276. https://doi.org/10.1111/j.1530-0277.2007.00578.x.
61. Kalange AS, Kokare DM, Singru PS, Upadhya MA, Chopde CT, Subhedar NK. Central administration of selective melanocortin 4 receptor antagonist HS014 prevents morphine tolerance and withdrawal hyperalgesia. *Brain Res.* 2007;1181:10-20. https://doi.org/10.1016/j.brainres.2007.08.054.
62. Starowicz K, Sieja A, Bilecki W, Obara I, Przewlocka B. The effect of morphine on MC4 and CRF receptor mRNAs in the rat amygdala and attenuation of tolerance after their blockade. *Brain Res.* 2003;990(1-2):113-119. https://doi.org/10.1016/s0006-8993(03)03444-9.
63. Chu H, Sun J, Xu H, Niu Z, Xu M. Effect of periaqueductal gray melanocortin 4 receptor in pain facilitation and glial activation in rat model of chronic constriction injury. *Neurol Res.* 2012;34(9): 871-888. https://doi.org/10.1179/1743132812y.0000000085.
64. Chu H, Xia J, Yang Z, Gao J. Melanocortin 4 receptor induces hyperalgesia and allodynia after chronic constriction injury by activation of p38 MAPK in DRG. *Int J Neurosci.* 2012;122(2):74-81. https://doi.org/10.3109/00207454.2011.630542.
65. Caruso V, Lagerström MC, Olszewski PK, Fredriksson R, Schiöth HB. Synaptic changes induced by melanocortin signalling. *Nat Rev Neurosci.* 2014;15(2):98-110. https://doi.org/10.1038/nrn3657.

66. Serova LI, Laukova M, Alaluf LG, Sabban EL. Intranasal infusion of melanocortin receptor four (MC4R) antagonist to rats ameliorates development of depression and anxiety related symptoms induced by single prolonged stress. *Behav Brain Res.* 2013;250:139-147. https://doi.org/10.1016/j.bbr.2013.05.006.
67. Fadok JP, Krabbe S, Markovic M, et al. A competitive inhibitory circuit for selection of active and passive fear responses. *Nature.* 2017;542:96-100. https://doi.org/10.1038/nature21047.
68. Funk CK, O'Dell LE, Crawford EF, Koob GF. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. *J Neurosci.* 2006;26(44):11324-11332. https://doi.org/10.1523/jneurosci.3096-06.2006.
69. Roberto M, Cruz MT, Gilpin NW, et al. Corticotropin releasing factor-induced amygdala gamma-aminobutyric acid release plays a key role in alcohol dependence. *Biol Psychiatry.* 2010;67(9): 831-839. https://doi.org/10.1016/j.biopsych.2009.11.007.
70. Valdez GR, Roberts AJ, Chan K, et al. Increased ethanol self-administration and anxiety-like behavior during acute withdrawal and protracted abstinence: Regulation by corticotropin-releasing factor. *Alcohol Clin Exp Res.* 2002;26(10):1494-1501.
71. Weera MM, Shackett RS, Kramer HM, Middleton JW, Gilpin NW. Central amygdala projections to lateral hypothalamus mediate avoidance behavior in rats. *J Neurosci.* 2021;41(1):61-72. https://doi.org/10.1523/jneurosci.0236-20.2020.
72. Baiamonte BA, Valenza M, Roltsch EA, et al. Nicotine dependence produces hyperalgesia: Role of corticotropin-releasing factor-1 receptors (CRF1Rs) in the central amygdala (CeA). *Neuropharmacology.* 2014;77:217-223. https://doi.org/10.1016/j.neuropharm.2013.09.025.
73. Secci ME, Holmgren E, Kasten C, Kelley L, Wills T, Gilpin NW. Adolescent alcohol exposure induces long-term hyperalgesia and alterations in CeA-PAG signaling in male and female rats. *Alcohol Clin Exp Res.* 2021;45(S1):148A.
74. Berkley KJ. Sex differences in pain. *Behav Brain Sci.* 1997;20(3): 371-380; discussion 435-513. https://doi.org/10.1017/s0140525x97221485.
75. Mogil JS, Bailey AL. Sex and gender differences in pain and analgesia. *Prog Brain Res.* 2010;186:141-157. https://doi.org/10.1016/b978-0-444-53630-3.00009-9.
76. Hurley RW, Adams MC. Sex, gender, and pain: An overview of a complex field. *Anesth Analg.* 2008;107(1):309-317. https://doi.org/10.1213/01.ane.0b013e31816ba437.
77. Da Silva JT, Tricou C, Zhang Y, Seminowicz DA, Ro JY. Brain networks and endogenous pain inhibition are modulated by age and sex in healthy rats. *Pain.* 2020;161(6):1371-1380. https://doi.org/10.1097/j.pain.0000000000001810.
78. Petersen KK, McPhee ME, Hoegh MS, Graven-Nielsen T. Assessment of conditioned pain modulation in healthy participants and patients with chronic pain: Manifestations and implications for pain progression. *Curr Opin Support Palliat Care.* 2019;13(2):99-106. https://doi.org/10.1097/spc.0000000000000419.
79. Davis DA, Luecken LJ, Zautra AJ. Are reports of childhood abuse related to the experience of chronic pain in adulthood? A meta-analytic review of the literature. *Clin J Pain.* 2005;21(5): 398-405. https://doi.org/10.1097/01.ajp.0000149795.08746.31.
80. Horn-Hofmann C, Trost Z, Hublet A, Mrug S, Van Damme J, Vervoort T. The relationship between pain severity and alcohol use among school-aged children and adolescents: The moderating role of drinking motives. *Pain Med.* 2018;19(2):284-296. https://doi.org/10.1093/pm/pnx016.

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Cognitive-Affective Transdiagnostic Factors Associated With Vulnerability to Alcohol and Prescription Opioid Use in the Context of Pain

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The use of alcohol and prescription opioids is common among people in pain and poses significant public health burdens. This review identifies factors associated with motivation to use alcohol and prescription opioids in the context of pain. Pain-relevant, cognitive-affective, transdiagnostic vulnerability factors—expectancies/motives, pain catastrophizing, pain-related anxiety, distress intolerance, anxiety sensitivity, and perceived interrelations—were selected from theoretical conceptualizations of pain and substance use. Searches conducted in PubMed, PsycINFO, and Embase returned 25 studies that examined associations between identified variables of interest and the use of alcohol and prescription opioids in the context of pain. Consistent with a larger literature on pain and substance use, the studies included in this review demonstrated that people with chronic pain are motivated to use alcohol and opioids in response to negative affect and hold expectancies/motives for coping with pain. Vulnerabilities that engender difficulty managing aversive internal states (distress intolerance and anxiety sensitivity) and maladaptive responses to pain (pain-related anxiety and pain catastrophizing) also were implicated in motivation for alcohol and opioid use. Although one study found that pain-related anxiety was associated with co-use of alcohol and opioids, no studies examined simultaneous use. Future research directions that can explicate causal associations, identify patterns of alcohol and opioid co-use, clarify the role of pain in cessation processes, and inform treatment development are discussed.

KEYWORDS: alcohol drinking; analgesics; opioids; pain; motivation; alcohol

Pain is a complex, near-universal phenomenon, which can be conceptualized as a motivational state that engenders goal-directed action.[1] Motivational models of substance use highlight the role of expected effects and suggest that individuals become motivated to use substances when such use is perceived as holding greater value than other available objects or events.[2,3] A rapidly growing empirical literature indicates that the use of substances, including alcohol and prescription opioids, may be a risk factor in the onset and progression of painful conditions, and that pain is a proximal determinant of acute substance administration and may serve as a barrier to cessation.[4–6] Accordingly, an evolving reciprocal model suggests that associations between pain and substance use are likely bidirectional in nature, resulting in the maintenance and worsening of both conditions over time.[4–6] A recent critical review highlighted emerging evidence that chronic pain frequently co-occurs with use of alcohol and opioids, and that co-use (i.e., use of both substances within a given timeframe) likely contributes to opioid overdose-related morbidity and mortality and worse substance-related treatment outcomes.[7] An important next step in this line of research is to identify potentially modifiable cognitive-affective factors that may underlie or exacerbate motivation to use alcohol and prescription opioids in the context of pain. A focus on processes that contribute to the onset, maintenance, or exacerbation of multiple psychiatric disorders (i.e., "transdiagnostic" factors) can further inform novel treatment targets and intervention development.[8,9]

The sections that follow begin with a brief overview of alcohol and opioid use, acute and chronic pain, and guiding theoretical frameworks. The results of studies that examined associations between pain, selected transdiagnostic cognitive-affective factors (derived from prominent theoretical conceptualizations of pain–substance use relations), and alcohol/prescription opioid use patterns/trajectories are then reviewed. Finally, the relevant extant literature is discussed with an emphasis on explicating clinical implications and generating recommendations to help guide future research in this emerging domain.

ALCOHOL AND PRESCRIPTION OPIOID USE

Prevalence and Impact

Approximately 50% of American adults consume alcohol each month,[10] and more than 25% endorse hazardous drinking (i.e., patterns of use associated with increased risk for harmful consequences).[11,12] Alcohol is implicated in nearly 100,000 deaths in the United States each year,[13] is the third leading cause of preventable death,[14] and has an annual economic impact of more than $250 billion in lost productivity, health care costs, and criminal justice expenses.[15] Although opioid prescribing has diminished somewhat in the wake of the opioid epidemic, nearly 20% of all Americans received an opioid prescription in 2017.[16] Nationally representative data further indicate that more than 12 million Americans misuse prescription opioids each year (i.e., use without a prescription or for a reason other than the purpose for which they were prescribed).[17] In the United States, prescription opioids are responsible for more than 15,000 overdose deaths[18] and for an economic burden of greater than $78 billion annually.[19] Although alcohol and prescription opioids have different pharmacokinetic profiles and substance-specific physiological/subjective effects, they may engender overlapping effects in the central and peripheral nervous systems, including activation of neural circuitry involved in pleasure and reward.[20] Both substances also are implicated in substance use disorders, which are characterized by maladaptive physiological (i.e., tolerance and withdrawal) and behavioral (e.g., impaired control over use behavior, social impairment as a result of use) consequences of use.[21]

Alcohol and Opioid Co-Use

Although definitions vary in the literature, in the context of alcohol and opioids, co-use may be characterized as concurrent use (i.e., within a given period of time, such as past month or past year) or simultaneous use (i.e., co-ingestion at the same time or in a closely overlapping period of time).[22–24] Despite contraindications for drinking alcohol while using prescription opioids, emerging data suggest that the prevalence of alcohol and opioid co-use is surprisingly high. For example, in samples recruited from primary care clinics, 36% of patients with a prescription for daily use of an opioid reported consuming alcohol in the last 30 days,[25] and 9% reported drinking to intoxication on up to 5 days in the past month.[26] Another study of patients on long-term opioid therapy found that 12% reported drinking alcohol within 2 hours of taking their medication.[27] Results from a community-derived sample further indicated that individuals who endorse prescription opioid misuse also report using alcohol at high rates, with up to 20% admitting to using alcohol and opioids in the same day.[28] Finally, nationally representative data indicate that individuals in the United States who meet diagnostic criteria for opioid use disorder (OUD) are nearly twice as likely to also meet criteria for alcohol use disorder (AUD), relative to individuals without OUD.[29] Both alcohol and opioids are central nervous system depressants, and any form of co-use could lead to dangerous, potentially fatal effects (e.g., liver damage, respiratory depression).[30] Indeed, co-use of alcohol was involved in 15% of deaths attributed to prescription opioid overdose in 2017.[31] In addition to heightened morbidity and mortality, a recent critical review found that co-occurring OUD and AUD were associated with poorer treatment outcomes for both disorders, with some evidence that alcohol consumption may increase during medication-assisted treatment for OUD.[7]

Prevalence and Impact of Pain

Although a handful of documented cases indicate a rare congenital inability to perceive pain,[32] pain is largely thought of as a universal human experience.[33] Pain is a highly prevalent public health burden that motivates 50% of annual physician visits in the United States,[34] with chronic pain engendering an annual economic impact of more than $600 billion in health care costs and lost productivity.[35] A recent update by the International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[36] This definition acknowledges that pain is a complex biopsychosocial phenomenon that involves an interplay of sensory-physiological, cognitive-affective, and behavioral processes, and that the experience of pain cannot be reduced to the activity of sensory neurons. As such, pain may persist beyond expected healing time or in the absence of identified tissue damage. The term chronic pain is typically used to describe pain lasting for at least 3 to 6 months,[37] and is distinguished from cancer-related pain, which differs in etiology and course.[38] More than 100 million Americans have a chronic noncancer pain diagnosis,[39] and recent nationally representative data indicate that on most days, nearly 20 million U.S. adults experience pain that interferes with activities of daily living.[40] The experience of pain commands attention and motivates action to avoid or limit bodily harm, often resulting in avoidance behaviors that can be adaptive in the short term (e.g., to promote healing).[1] However, long-term cycles of maladaptive cognitive-affective responses that lead to persistent avoidance (e.g., worry that pain will never end) are thought to be a predominant cause of pain-related disability.[41] Indeed, chronic pain can have significant negative effects on quality of life and emotional well-being, including interference in occupational functioning,

recreational activities, relationships, self-care, physical activities, and sleep.[42]

Co-Occurring Pain and Use of Alcohol and Opioids

The extant literature suggests that pain co-occurs at high rates with both alcohol and opioid use, potentially in a dose-dependent fashion.[6] With regard to alcohol use, individuals with chronic pain endorse higher rates of hazardous drinking and are up to two times more likely than the general population to meet criteria for AUD.[6,39,43] Greater levels of pain severity[44] and functional interference have been associated with an increased likelihood of engaging in hazardous drinking patterns and meeting diagnostic criteria for AUD,[45] respectively. Pain also appears to be more common among individuals who report hazardous alcohol use: 43% of people who experience drinking problems (e.g., adverse consequences or life problems as a result of drinking) and 75% of individuals with AUD have been shown to endorse current moderate to severe pain (vs. 18% in the general population).[46–48] The co-occurrence of pain and prescription opioid use is intuitive given that opioids are prescribed for pain relief, though pain is also common among individuals who report use of opioid analgesics without a prescription.[49–51] A review of pain and prescription opioid misuse found that 49% to 96% of patients seeking treatment for prescription opioid misuse reported chronic pain, and that 82% reported pain as their reason for initiating opioid misuse.[52] This review further observed a positive association between pain severity and opioid misuse, such that even among patients with chronic pain, pain ratings tended to be higher among those who reported prescription opioid misuse or who met criteria for OUD.

GUIDING THEORETICAL FRAMEWORKS

Pain Processing and Negative Reinforcement

Pain is an inherently aversive experience that reliably elicits negative affect and motivates escape/avoidance behaviors.[1,41] Consistent with biopsychosocial conceptualizations of pain, the four-stage model of pain processing posits that negative affect mediates behavioral responses to pain.[4,53] More specifically, this model invokes both acute negative affect (e.g., distress) that is elicited from the immediate sensory experience as well as extended pain affect (e.g., depression, anxiety) that manifests in the context of chronic pain and functional impairment. Both forms of pain-related negative affect are considered sufficient to motivate adaptive and/or maladaptive behavioral efforts to cope with pain; substance use has been identified as a commonly employed maladaptive pain coping response;[4,54] and efforts to modulate affect have been implicated in pain and substance use trajectories.[41,55] Negative reinforcement—the process by which behavioral responses that are perceived to alleviate aversive states become more likely or increase in frequency—is a core component of theoretical models of both pain and substance use.[1,55] Researchers have further hypothesized that as attempts to avoid/reduce pain or negative affect via substance use are reinforced, the use of substances as a primary coping strategy may become more entrenched over time.[5]

Reciprocal Model of Pain and Substance Use

In drawing upon motivation theory, negative reinforcement frameworks, and the four-stage model of pain processing, a leading reciprocal model posits that pain and substance use interrelate in the manner of a positive feedback loop, resulting in more severe pain, greater functional impairment, and the maintenance of addiction.[4,5] Within this model, the substance use–to–pain pathway acknowledges that although substances such as alcohol and opioids can reduce

pain in the short term, chronic substance use has been identified as a unique risk factor in the onset and progression of hyperalgesia (i.e., increased sensitivity to painful stimuli) and persistently painful conditions.[56–60] In the pain–to–substance use pathway, which is most germane to the current review, pain is conceptualized as a potent motivator of substance use. Pain severity has consistently been associated with use of multiple substances (e.g., nicotine/tobacco, cannabis, alcohol),[5] and human experimental research has shown that pain and pain-related negative affect can increase craving and motivate substance use.[61–63] Indeed, the role of pain as a proximal antecedent to substance use is of growing empirical interest, as highlighted by a recently published Catastrophizing, Anxiety, Negative Urgency, and Expectancy (CANUE) model that emphasizes the influence of negative affect in motivation to self-medicate one's pain with a variety of addictive substances.[64] Thus, the reciprocal model of pain and substance use predicts that acute pain serves as a proximal determinant of substance use behavior, and that via repeated exposures and reinforcement, relations between pain and substance use may become more robust in the context of chronic or persistent pain.[5]

Use of Alcohol and Prescription Opioids in the Context of Pain

Given the high degree of co-occurrence and significant individual/societal costs associated with alcohol and prescription opioid use, the goal of this review is to explicate potentially modifiable factors that are associated with motivation to use and co-use alcohol and prescription opioids in the context of pain.[4,5,64] The need to examine pain as a determinant of alcohol and prescription opioid use is further supported by evidence that nearly 25% of patients enrolled in both pain and inpatient substance use treatment programs have endorsed using alcohol to cope with pain, with many citing pain as the primary impetus for hazardous drinking and other substance use.[65,66] Similarly, a systematic review of opioid misuse and chronic pain found that approximately 21% to 29% of patients prescribed opioids for chronic pain engage in misuse (i.e., use other than prescribed).[67] The CANUE model further suggests that people with chronic pain may be most motivated to self-medicate with substances when they also hold maladaptive pain-related cognitions or are otherwise vulnerable to impulsive behavior when distressed.[64] Indeed, researchers have highlighted several cognitive-affective transdiagnostic constructs (e.g., expectancies, pain-related anxiety, distress intolerance) implicated in the development, maintenance, and exacerbation of bidirectional relations between pain and substance use.[5,9,64]

METHOD

Selection of Relevant Constructs

The constructs of interest in this review were derived from theoretical frameworks of motivation and pain–substance use relations, with a focus on cognitive-affective constructs that are hypothesized mechanisms of the pain–to–substance use pathway and have been implicated as vulnerabilities to multiple psychiatric disorders.[5,9,64] Of particular interest were constructs that are hypothesized causal mediators by which the acute pain experience may serve as a proximal determinant of substance administration, or constructs that may function as moderators (e.g., exacerbating or amplifying existing determinants) or serve to make substance use more salient or incentivized in the context of pain. Modifiable cognitive-affective constructs (briefly described below) were selected as the focus because these constructs have the potential to serve as integrated behavioral targets and to better inform future research and intervention development efforts.

Expectancies, Motives, and Perceived Interrelations

For the current review, expectancies, motives, and perceived interrelations broadly refer to the extent to which people perceive associations between their pain and substance use.[2,5] Whereas

expectancies represent beliefs about what will happen as a result of substance use, motives represent the desired results (i.e., self-reported reasons and valued/desired effects) of substance use.[68] Perceived interrelations further encompass perceptions regarding the co-occurrence and bidirectional effects of pain and substance use.[69]

Pain-Related Anxiety and Pain Catastrophizing

Pain-related anxiety is the tendency to respond to actual or anticipated pain with anxiety or fear, which may motivate avoidance behaviors.[70,71] Similarly, pain catastrophizing reflects the tendency to interpret actual or anticipated pain in an exaggerated manner.[72] The contributions of pain-related anxiety and pain catastrophizing to the onset and maintenance of chronic pain are well recognized.[33] More recently, theoretical models of pain and substance use have included pain-related anxiety and pain catastrophizing as transdiagnostic factors that are also relevant to multiple substance-related outcomes (e.g., craving, heaviness of use, cessation) among people with chronic pain.[5,9,73–75]

Anxiety Sensitivity

Anxiety sensitivity (defined as fear of the potential negative consequences related to anxiety-related symptoms and sensations)[76] is another transdiagnostic factor that is likely relevant to pain–substance use reciprocity.[9] Research has demonstrated independent, positive associations between anxiety sensitivity and heavy/problematic substance use[77,78] and greater pain impairment/persistence.[79–81] There is also evidence that greater anxiety sensitivity may contribute indirectly to the association between pain and poorer outcomes related to substance use and health.[82]

Distress Intolerance

Distress intolerance also may contribute to pain and substance use reciprocity. Research has consistently demonstrated positive associations between distress intolerance (defined as the perceived inability to tolerate negative emotional and/or other aversive states),[83] substance addiction, and poorer cessation/treatment outcomes, including drug and alcohol treatment dropout and substance use relapse.[84,85] There is also evidence that levels of distress intolerance may be higher among individuals with co-occurring pain (vs. no pain in the past month)[86] and that individuals with high distress intolerance are more likely to endorse substance coping motives.[87–89]

Search Strategy and Study Selection

Literature searches were conducted in PubMed, PsycINFO, and Embase using the terms alcohol drinking OR alcohol-related disorders OR analgesics, opioid OR opioid-related disorders; pain; and expectancies OR motives OR perceived interrelations OR negative affect OR pain-related anxiety OR catastrophizing OR anxiety sensitivity OR distress intolerance. All search criteria were limited to human species and peer-reviewed journals published in English before December 2020. Searches yielded 124 unique records after duplicates were removed. Given this review's focus on the pain–to–substance use pathway, the authors sought to identify studies that examined alcohol/opioid criterion variables in relation to at least one of the selected constructs. They included studies that utilized pain-related predictor variables (e.g., pain intensity) or were conducted among relevant pain populations (e.g., chronic pain, persons living with HIV). Studies conducted among healthy, non–treatment-seeking samples were included only if (a) the sample was necessary to answer a pain-related research question (e.g., laboratory experimental pain studies that require healthy participants), and (b) the study included at least one other variable of interest. Primary reasons for exclusion were (a) it was not a behavioral study of the pain–to–substance use pathway (81 studies) or not a relevant population (32 studies).

RESULTS

Twenty-five studies were identified for inclusion (see Table 1).

Table 1 References Identified in Literature Search ($N = 25$), by Variable of Interest

Reference	Author	Year	Design	Outcome(s)
Expectancies, Motives, and Perceived Interrelations				
90	Palfai et al.	2019	Cross-sectional	Alcohol Use
91	Nieto et al.	2020	Cross-sectional	Alcohol Use
92	LaRowe, Maisto, & Ditre	2021	Cross-sectional	Alcohol Use
Negative Affect				
93	Moskal et al.	2018	Experimental	Alcohol Use
94	Witkiewitz et al.	2015	Longitudinal	Alcohol Use
95	Carpenter et al.	2019	EMA*	Opioid Use
96	Finan et al.	2018	Daily Diary	Opioid Use
Pain-Related Anxiety				
73	Zale et al.	2019	Cross-sectional	Alcohol Use
97	Rogers et al.	2018	Cross-sectional	Opioid Use
98	Rogers et al.	2020	Cross-sectional	Opioid Use
99	Rogers et al.	2020	Cross-sectional	Opioid Use
100	LaRowe et al.	2018	Cross-sectional	Opioid Use
111	LaRowe et al.	2020	Cross-sectional	Alcohol Opioid Co-Use
Pain Catastrophizing				
91	Nieto et al.	2020	Cross-sectional	Alcohol Use
101	Lee et al.	2020	Cross-sectional	Opioid Use
96	Finan et al.	2018	EMA*	Opioid Use
102	Martel et al.	2014	Cross-sectional	Opioid Use
103	Arteta et al.	2016	Cross-sectional	Opioid Use
104	Martel et al.	2013	Cross-sectional	Opioid Use
112	Votaw et al.	2020	Cross-sectional	Alcohol Use, Opioid Use
Anxiety Sensitivity				
105†	Rogers et al.	2019	Cross-sectional	Opioid Use
106†	Smit et al.	2020	Cross-sectional	Opioid Use
78†	Rogers et al.	2019	Cross-sectional	Opioid Use
107†	Rogers et al.	2020	Cross-sectional	Opioid Use
108	Rogers et al.	2020	Cross-sectional	Opioid Use
Distress Intolerance				
110	McHugh et al.	2014	Cross-sectional	Opioid Use

* EMA, ecological momentary assessment.

† Studies were drawn from the same sample.

Pain as a Motivator of Alcohol Use

Expectancies, motives, and perceived interrelations

Initial qualitative and cross-sectional evidence suggest that people with chronic pain hold unique cognitions about how pain and alcohol use are related. First, a qualitative study of 10 people living with HIV who had chronic pain and reported heavy drinking (i.e., more than four or five drinks on one occasion or more than seven to 14 drinks per week for women/men) provided evidence that alcohol may be seen by people with chronic pain as a primary means of coping with both pain and pain-related distress.[90] A theme emerged in which alcohol was perceived by the participants to be a "harmless alternative" to prescription opioids for pain management. Among a sample of patients seeking treatment for AUD ($N = 128$), high-intensity pain ratings (vs. no or low-intensity pain) were associated with a greater number of self-reported drinks per day and higher alcohol craving, and participants with high-intensity pain were more likely to report normalizing motives for drinking (i.e., "to feel normal").[91] Finally, researchers recently developed and validated the Expectancies for Alcohol Analgesia measure, which assesses perceived likelihood of pain relief from drinking. In a sample of 273 people who reported chronic pain and current alcohol use, expectancies for analgesia were associated with reporting greater frequency and quantity of alcohol use and identifying coping as a motive for drinking.[92]

Negative affect

Consistent with the larger substance use literature and theoretical conceptualizations of negative affect as a primary motivator of substance use behavior,[3,5,64] there is experimental and observational evidence that the experience of pain, by eliciting negative affect, is a proximal determinant of alcohol use. Laboratory models of human pain utilize standardized noxious stimuli that attempt to approximate features of clinical pain conditions (e.g., neuropathic pain, musculoskeletal pain), reliably elicit sensory pain and subjective distress, and have successfully been used to investigate causal associations between pain and tobacco smoking.[60,61] A recent laboratory experiment conducted among hazardous drinkers further provides causal evidence that pain increases motivation to drink alcohol.[93] Specifically, participants randomized to laboratory pain induction (vs. no pain) reported greater negative affect, which in turn was associated with a greater urge and intention to drink. Prospective evidence derived from two multisite clinical trials for AUD (in the United States and the United Kingdom) provides further evidence that negative affect is a determinant of drinking in the context of pain.[94] Across both samples ($N = 2,125$), pain severity at the end of treatment predicted frequency and quantity of alcohol use at long-term (9- to 12-month) follow-up. Moreover, pain predicted increased negative affect, which mediated the effect of pain on drinking outcomes.

Pain-related anxiety

Although several studies have implicated pain-related anxiety in associations between pain and other substances (e.g., tobacco, cannabis),[5] the search for this review returned only one study that examined associations between pain-related anxiety and alcohol use. In an online survey of 234 adults with chronic pain, pain-related anxiety was positively associated with alcohol-related consequences (e.g., injuries from drinking, blackouts) and impairment in functioning due to alcohol use (i.e., needing a drink in the morning, inability to stop drinking once started, and failure to fulfill obligations due to drinking).[73] Moderation analyses further revealed that associations between pain-related anxiety and drinking were significant among men, but not women.

Pain catastrophizing

Like pain-related anxiety, pain catastrophizing has been widely studied in relation to tobacco smoking and cannabis use.[5,64] However, the authors identified only one study that tested associations between pain catastrophizing and alcohol use outcomes. That study, which tested associations between pain and alcohol consumption and motives among 128

patients seeking AUD treatment, also examined pain catastrophizing as a predictor variable of all outcomes.[91] Results indicated that pain catastrophizing was associated with greater alcohol craving, AUD symptoms, and normalizing drinking motives, regardless of pain intensity.

Pain as a Motivator of Prescription Opioid Use

Negative affect

Initial evidence suggests that negative affect mediates proximal associations between pain and prescription opioid use, similar to alcohol use. Although the search did not return any experiments that tested causal association between pain and opioid use in humans, prospective studies that utilized repeated assessments provide evidence for the effects of pain on prescription opioid use via negative affect. First, real-time ecological momentary assessment among 34 patients on long-term opioid therapy for chronic pain indicated that, over the 2-week assessment period (2,285 total observations), patients were more likely to report opioid use during occasions of increased pain, and they consumed higher doses when pain was accompanied by increased negative affect.[95] Similar results were observed in a daily diary study of patients with pain due to sickle cell disease who were prescribed opioids ($N = 45$). Over the 90-day assessment period, greater levels of pain and negative affect were individually associated with use of opioids at higher doses during the same day, although negative affect was not statistically tested as a mediator.[96]

Pain-related anxiety

Results from several cross-sectional studies suggest that pain-related anxiety is associated with multiple indices of prescription opioid misuse among people with chronic pain. First, in an online survey of young adults ($N = 256$) who endorsed moderate to severe past-month pain, greater pain-related anxiety was associated with increased likelihood of self-reported addiction to opioids, history of family concern about opioid use, past use of opioid detoxification, and more opioid-related problems.[97] Similarly, a study of 164 adults with obesity and chronic pain found that pain-related anxiety was associated with opioid misuse.[98] In a cross-sectional survey of nearly 400 adults with chronic pain, pain-related anxiety was identified as a statistical mediator of associations between pain severity and opioid misuse.[99] Finally, in a clinical sample of 61 smokers of tobacco cigarettes living with HIV and recruited from an infectious disease clinic, higher levels of pain-related anxiety were associated with current opioid misuse among men, but not women.[100]

Pain catastrophizing

Several studies conducted among treatment-seeking chronic pain samples consistently demonstrated positive associations between pain catastrophizing and prescription opioid use. First, among a sample of 51 patients with chronic pain, two facets of pain catastrophizing were positively associated with higher scores on a measure of risk for opioid misuse.[101] Specifically, rumination (i.e., the tendency to have difficulty disengaging from pain-related cognitions) and magnification (i.e., the tendency to magnify perceptions of threat) were each individually associated with risk of opioid misuse. There was also evidence that pain catastrophizing was associated with more frequent cravings for opioids, regardless of pain intensity.[102] Similarly, a daily diary study revealed that people with chronic pain maintained on opioid therapy used higher dosages of their prescription opioids on days in which self-reported catastrophizing was higher, even when pain was low.[96] In addition, two cross-sectional studies conducted among patients maintained on opioid therapy for chronic pain demonstrated evidence of negative affect as a statistical mediator of associations between pain catastrophizing and opioid misuse.[103,104]

Anxiety sensitivity

Among an online sample of 429 adults who self-reported moderate to severe chronic pain and prescription opioid use, anxiety sensitivity mediated associations between greater

pain intensity and opioid misuse and OUD symptoms[105,106] and was associated with greater likelihood of endorsing use of opioid medications "to get high."[78] In the same sample, models of indirect effects indicated that negative affect was associated with opioid misuse through anxiety sensitivity.[107] Interestingly, when the model was run in reverse, equal statistical support was observed for an indirect effect of anxiety sensitivity via negative affect, suggesting that prescription opioid misuse may occur in the context of a complex interplay between negative affect and anxiety sensitivity. Finally, data derived from an online sample of nearly 300 adults who reported chronic low back pain indicated that anxiety sensitivity may have an indirect effect on risk of opioid misuse through greater coping and pain management motives for prescription opioid use.[108]

Distress intolerance

Distress intolerance previously has been associated with tobacco and cannabis use among people with chronic pain and has been implicated in heavy drinking and alcohol-related problems in healthy populations.[5,109] However, only one cross-sectional study that investigated associations between distress intolerance and prescription opioid use was identified. Among a sample of 39 patients at a pain management clinic who were prescribed opioids, greater levels of distress intolerance were associated with greater scores on a measure of opioid misuse risk, even after statistical analyses controlled for pain intensity.[110]

Pain as a Motivator of Alcohol and Opioid Co-Use

Although co-use of alcohol and opioids has potentially dire health consequences, this review identified only one study that directly examined alcohol and prescription opioid co-use in the context of chronic pain. In an online sample of 1,812 adults with chronic low back pain, 12% endorsed use of both alcohol and prescription opioids (co-use) and 3% met cut-offs for both hazardous drinking and opioid misuse in the past month (i.e., concurrent use).[111] Pain-related anxiety was individually associated with hazardous alcohol use, opioid misuse, and likelihood of alcohol and opioid co-use. Moreover, every 1-point increase in pain-related anxiety was associated with a 4% increase in likelihood of concurrent hazardous drinking and opioid misuse. Another recently published study, which examined polysubstance use (defined as use of more than one substance in the month before treatment) among a subsample of 236 people receiving inpatient treatment for AUD or OUD who reported chronic pain, showed that the two most commonly reported substances were alcohol and prescription opioids.[112] Separate statistical models further indicated that pain-related interference with functioning was associated with a greater number of substances used among men (but not women) and among people with AUD (but not people with OUD). No associations were observed between pain catastrophizing and number of substances used.

DISCUSSION

Prior research has demonstrated that pain motivates substance use and may contribute to the maintenance of addiction.[5,6,64] The purpose of the current review was to examine modifiable cognitive-affective factors that may be associated with motivation to use alcohol and prescription opioids in the context of pain. These constructs include key mechanisms in motivational models of both substance use and pain (negative affect, expectancies/motives)[2,113] and factors in the reciprocal model of pain and substance abuse (pain-related anxiety, pain catastrophizing, distress intolerance, and anxiety sensitivity) that may increase vulnerability to both conditions.[5,9,64] Consistent with a reciprocal model of pain and substance use, this review provides evidence that pain is a proximal determinant of alcohol use[114] and opioid use,[95] even among individuals without chronic pain.[114] The review further observed consistent evidence that people with chronic pain are motivated to use alcohol and prescription opioids in response to negative affect[94,95] and maladaptive pain-related cognitions

(e.g., catastrophic thinking).[91,100] Finally, this review found initial evidence suggesting that difficulty managing aversive internal states is associated with risk for opioid misuse,[110] and that people with chronic pain hold unique motives and perceptions about how their pain and drinking are interrelated.[90]

Motivational models of both pain and substance use highlight the role of negative affect as a primary determinant of escape/avoidance behaviors, and negative reinforcement is likely a key mechanism by which pain motivates and ultimately maintains substance use.[5,64] The current review provides some support for this perspective, with experimental and real-time evidence from three studies indicating that negative affect mediates associations between the experience of pain and acute bouts of alcohol and prescription opioid use.[93,95,96] The authors also reviewed three studies that provided cross-sectional evidence of covariation between negative affect and transdiagnostic vulnerability factors, such that negative affect was a statistical mediator of associations between opioid misuse and both pain catastrophizing[103,104] and anxiety sensitivity.[107] Initial evidence from one study further suggests that difficulty with tolerating negative affect (i.e., distress intolerance) is associated with opioid misuse.[110] Taken together, these findings lend support to the notion that people may experience greater motivation to use alcohol and prescription opioids during heightened states of acute and extended pain affect, and that such effects may be amplified in the context of transdiagnostic vulnerability factors that exacerbate (e.g., pain catastrophizing) or diminish capacity for coping with (e.g., distress intolerance) negative affect.

Pain-related anxiety and pain catastrophizing are both thought to motivate maladaptive attempts to avoid or alleviate pain.[115] Consistent with evidence that both prescription opioids and alcohol have acute analgesic effects, the current review provides initial evidence that people who experience chronic pain may view drinking alcohol as a viable approach to pain management[90] or hold expectancies for pain relief from drinking.[92] The review also observed consistent evidence across several studies that pain-related anxiety and pain catastrophizing are associated with alcohol and opioid use among people with chronic pain.[73,96,102,111] Maladaptive cognitive-affective responses to pain may activate escape/avoidance processes, leading to use of alcohol and/or opioids. These observations are in line with conceptual models of pain and substance use and further support consideration of pain-related cognitions as potentially key transdiagnostic vulnerability factors for alcohol and opioid use.[5,9,64]

Although both alcohol and prescription opioids present health risks when used individually, co-use is associated with increased morbidity and mortality and presents a significant public health threat.[7] Despite the dangers of concurrent use of alcohol and opioids, the authors found only one study that was designed to examine co-use of these substances in the context of pain.[111] Consistent with findings from studies of either substance alone, pain-related anxiety was associated with greater likelihood of misuse of both substances concurrently in an online sample of adults with chronic pain. One potential explanation for this finding is that people with higher levels of pain-related anxiety may view concurrent use as a way to extend or supplement analgesic effects of both substances.[116] Although there is reason to suspect that alcohol-opioid co-use also could be seen as a more potent means of escaping/avoiding negative affect (vs. use of either substance alone), this hypothesis is yet to be tested.

Limitations and Future Directions

Studies included in the current review consistently yielded evidence suggesting that negative affect and other maladaptive cognitive-affective responses to pain and distress may cause alcohol and prescription opioids to take on greater salience in the context of pain. As shown in Table 1, this review identified one experimental study and three prospective studies that lend support regarding temporal precedence; however, the majority of reviewed studies were cross-sectional in nature and thus preclude causal interpretations. Future research would benefit from employing experimental and prospective designs to identify causal relationships and monitor covariation between pain-relevant cognitive-affective

constructs and the use or co-use of alcohol and/or opioids over time. For example, prospective studies may test whether maladaptive responses to pain predict escalation of alcohol and/or opioid use or the development of AUD and/or OUD. Ecological momentary assessment provides a promising avenue for assessment of alcohol and opioid co-use in real time and should be considered as a means of better understanding simultaneous use. Indeed, despite the dangers of being under the influence of alcohol and opioids at the same time, the current review did not identify any studies that have investigated motivation for simultaneous use in relation to this review's constructs of interest. Although dichotomous co-use status (yes/no) provides utility at this early stage of hypothesis testing, co-use should be assessed in greater detail (e.g., frequency, quantity, experience of negative consequences, and temporal proximity of alcohol and prescription opioid ingestion). Particular attention should be paid to identifying patterns of heavy drinking (e.g., frequency, quantity) and prescription opioid use (e.g., high dose, prolonged release, and once-daily formulation) that may increase risk of overdose or other harmful effects.[31,117] Research in this area should include a focus on both overlapping and distinct pharmacologic effects of alcohol and prescription opioids.

Future research also is needed to better understand motivation to use alcohol and prescription opioids in the context of other comorbidities. First, co-use of alcohol and opioids with other substances (e.g., nicotine, cannabis)—particularly those that increase risk for medical consequences and public health burden—should be examined. For example, 22% of opioid-related overdose deaths involve co-use of alcohol, opioids, and benzodiazepines.[118] Up to 23% of chronic pain patients prescribed opioids also hold a concurrent prescription for a benzodiazepine,[119] and risk of opioid-related overdose death among this group is 10 times greater than among those who hold an opioid prescription alone.[120] Anxiolytic properties of benzodiazepines may further encourage use as a method to escape/avoid pain and negative affect. Similar considerations regarding temporal precedence and the need for comprehensive assessment of dynamic substance use patterns should be applied to the study of polysubstance use in the context of pain. This review's transdiagnostic approach, which focuses on vulnerability factors implicated in a range of psychiatric conditions (e.g., depression, post-traumatic stress disorder, anxiety, personality disorders),[121–124] also highlights the complexity and interrelatedness of pain, substance use, and psychiatric comorbidities. Future research should seek to identify additional vulnerability factors that may contribute to or exacerbate relations between pain and use or co-use of alcohol or prescription opioids. For example, separate literatures have shown bidirectional relationships between sleep disturbances (e.g., difficulty falling or staying asleep) and both substance use[125] and pain;[126] researchers should consider a range of behavioral and psychiatric comorbidities when studying alcohol and prescription opioid use in the context of pain. Finally, the majority of included studies focused on a single construct of interest, and additional studies should be conducted to examine interrelations and unique contributions of the constructs examined in this review. Indeed, several studies examined negative affect as a statistical mediator of associations between cognitive-affective factors (i.e., anxiety sensitivity, catastrophizing) and opioid use,[103,104,107] and only one study tested associations between a cognitive-affective variable and self-reported motives for opioid use.[108] Future research is needed to disentangle likely complex and bidirectional associations between this review's variables of interest.

Given the central role of motives and expectancies in motivational models of substance use,[3] the authors were surprised to find a paucity of studies that examined expectancies and motives using validated measures (e.g., the Alcohol Expectancy Questionnaire[127]). Albeit limited, data from this review are in line with the larger literature suggesting that people with chronic pain hold substance-related outcome expectancies for pain relief and coping.[5] Recent validation of the

Expectancies for Alcohol Analgesia scale provides evidence that people with chronic pain can reliably self-report expectancies for pain relief from alcohol and that perceived likelihood of analgesic effects may motivate greater frequency and/or quantity of drinking.[92] In addition to coping, future research is needed to identify other types of motives and expectancies that may motivate substance use in the context of pain. For example, chronic pain often results in decreased social functioning, and researchers have hypothesized that social drinking motives may be particularly salient as a means of reducing pain-related interference in social functioning.[6] Similarly, as chronic pain interferes with occupational, social, and recreational functioning, people who have high levels of pain-related disability often lose access to other positive reinforcers.[4] A key component of incentive motivation models involves weighing the incentive value of substance use against other incentives available in the environment.[2,113] For people with chronic pain, expectancies regarding the positive reinforcing effects (e.g., to feel good or high) may become particularly salient. Future research should assess a range of expectancies and motives (including and beyond coping with pain and direct pain reduction) for alcohol, opioids, and co-use of both substances among people with chronic pain. Future research also would benefit from examining the role of positive affect and positive reinforcement processes in bidirectional alcohol and opioid use processes.

Although only a few included studies examined sex/gender differences, this review did observe initial evidence that pain and pain-related constructs may hold greater motivational salience for alcohol and prescription opioid use among men, relative to women. Future research should investigate reasons why men may be more motivated to use substances in the context of pain. For example, men and women likely experience varying pharmacologic effects of alcohol and opioids as a function of biological sex,[128] and it may be that men derive greater analgesia from use or co-use of alcohol and prescription opioids.[129] Considering gender as a biopsychosocial construct,[130] there is reason to suspect that men and women experience pain and substance use differently. For example, masculine norms may influence which pain-related behaviors are most common or accessible to men,[131] which is consistent with a larger literature indicating that men are more likely than women to cope with pain and anxiety by using externalizing strategies.[132,133] Thus, future studies that consider pharmacokinetic properties of prescription opioids and alcohol should examine sex as a biological variable, and research that investigates psychosocial and behavioral constructs should explore gender differences. Although the findings presented in the current review may have been drawn from cisgender samples, future research should test associations between pain and substance use among transgender and gender minority populations.[134,135] Additionally, despite documented racial/ethnic disparities in the prevalence, treatment, and outcomes of pain-related conditions,[136,137] this review identified only one study that examined the current constructs of interest among racial/ethnic minorities.[97] A recent review of racial and ethnic disparities in chronic pain treatment found that Black patients maintained on long-term opioid medication were more closely monitored for misuse, despite higher rates of opioid misuse and opioid-related overdose deaths observed among Whites.[138] Furthermore, racial and ethnic minorities, including Native Americans, Blacks, and Hispanics, are disproportionately impacted by drinking, including greater alcohol-related problems and reduced access to treatment, compared to Whites.[139] Initial evidence derived from the tobacco literature suggests there may be important racial/ethnic differences in associations between cognitive-affective constructs, pain experience, and substance use.[140] Future research would benefit from examining disparities as a function of social/cultural characteristics, racial/ethnic discrimination, and economic disadvantage, among others.

Finally, this review identified studies that predominantly focused on motivational processes in the context of ongoing substance use. Additional research is needed to better understand whether cognitive-affective and transdiagnostic vulnerability factors are also associated with

motivational processes in the context of substance-related cessation, reduction, and abstinence. For example, several constructs (e.g., pain-related anxiety) previously were associated with relapse to tobacco smoking among people with chronic pain.[75] Although this review identified one study that examined long-term outcomes after participation in treatment for AUD, the authors are not aware of any work that has directly tested these constructs in relation to lapse/relapse trajectories for alcohol and/or prescription opioid use. Consistent with a phase-based approach to treating substance use,[141] research should focus on the full spectrum of substance use outcomes rather than on long-term cessation rates alone. Future research also should seek to identify the extent to which expectancies for pain relief and cognitive-affective responses to pain may be related to motivation to quit or reduce use or co-use of alcohol and prescription opioids, or whether such factors influence differential acceptance of referral to alcohol treatment or to programs for tapering prescription opioid use.

Clinical Implications

Although based on a relatively nascent empirical literature, the current review highlights the importance of assessing pain when treating alcohol and prescription opioid use. Integrated treatments may be especially useful for addressing co-occurring pain and substance use because, relative to traditional approaches (e.g., distinct treatments for individual disorders delivered sequentially), they can be more efficient and cost-effective and can focus on both conditions as treatment targets.[142] The currently reviewed cognitive-affective constructs represent intuitive targets for integrated treatments because of their likely transdiagnostic role in both substance- and pain-related processes across multiple disorders. Indeed, substance use interventions that address transdiagnostic vulnerabilities (e.g., anxiety sensitivity) are well underway,[143,144] and this work should be extended to the domain of alcohol and opioid use or co-use. Several evidence-based techniques have been used to address maladaptive appraisals of pain and negative affect, including cognitive restructuring (i.e., development of balanced, adaptive thought patterns),[145] graded exposure to pain and distress-eliciting stimuli (i.e., to reduce escape/avoidance behaviors),[146,147] and coping skills training (e.g., skills to tolerate distress and pain without substance use).[148–150] In addition, integrated behavioral interventions may be utilized in concert with pharmacotherapy, and several pharmacotherapies that are commonly used for pain management (e.g., gabapentin, bupropion) are under investigation for their utility in the treatment of alcohol use and misuse.[151–153] Future work should consider whether there may be synergistic benefit to including pharmacotherapy in integrated interventions for pain and substance use.

Motivational enhancement interventions that target treatment engagement (e.g., willingness to accept a referral for opioid tapering) and motivation to reduce or abstain from alcohol and opioid use also are needed. Although interventions to increase awareness of opioid overdose risk behaviors have been developed,[154,155] the authors are not aware of any treatments that address alcohol and opioid co-use in the context of pain. An integrated treatment for alcohol and opioid use could focus on increasing knowledge regarding adverse interrelations between pain, alcohol, and opioids; increasing motivation and intention to reduce hazardous alcohol use and misuse of opioid medications; and reducing intentions to co-use alcohol and prescription opioid medications. Consistent with a motivational enhancement approach, an important intervention component would be to make an explicit link between continued alcohol/opioid use and poorer pain outcomes, and to highlight pain-related benefits of cessation (i.e., clinically meaningful improvements in pain and interference have been documented after reducing hazardous drinking[6,156] and opioid tapering[157]).[158] Indeed, recent studies derived from the tobacco literature suggest that chronic pain patients may be motivated to reduce their substance use once they perceive a discrepancy between continued substance use and desired pain outcomes.[159,160]

Finally, personalized feedback interventions (PFIs) are a subset of motivational interventions that

show greater promise for treating co-occurring pain and substance use, and can be delivered via scalable treatment modalities (e.g., computer-delivered interventions, smartphone applications).[161] PFIs motivate behavior change via psychoeducation and presentation of feedback about personal behavior (e.g., risk severity) in normative comparison to others (e.g., from relevant sociodemographic groups).[162,163] Parallel lines of inquiry indicate that PFIs decrease maladaptive cognitive-affective and behavioral responses to pain,[164,165] and that they reduce hazardous drinking as well as progression to and maintenance of AUD.[166,167] Two recent studies from the tobacco literature indicated that a brief, single-session computerized PFI is sufficient to increase knowledge of interrelationships between pain, opioid use, and smoking[168] and motivation/intention to quit smoking.[159] Computerized or smartphone-based PFIs can be integrated efficiently with self-monitoring and momentary assessment tools to provide immediate or same-day personalized feedback or just-in-time adaptive interventions (i.e., delivery of intervention content that has been adapted based on time-varying factors, including the state of vulnerability and receptivity to support), and can be used to increase treatment engagement.[164,169,170] These results provide support regarding the potential of integrated PFI interventions for pain, alcohol, and opioids.

CONCLUSIONS

Chronic pain and use of alcohol and prescription opioids co-occur frequently, and pain is a potent motivator of alcohol and opioid use. People with chronic pain may be motivated to use alcohol and opioids in response to negative affect or in response to expectancies/motives for pain coping. Transdiagnostic vulnerabilities for maladaptive responses to pain (pain-related anxiety, pain catastrophizing) and difficulty managing or tolerating aversive states and negative affect (distress intolerance, anxiety sensitivity) also may motivate alcohol or opioid use in the context of pain. Future research should examine the role of transdiagnostic factors in motivating patterns of alcohol or opioid use or co-use over time (e.g., escalations in frequency/quantity of use, lapse/relapse trajectories). Integrated interventions for alcohol and prescription opioid use that address pain-relevant, cognitive-affective processes (e.g., motivation for escape/avoidance of pain or negative affect) also should be developed and tested.

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References

1. Vlaeyen JWS, Crombez G. Behavioral conceptualization and treatment of chronic pain. *Annu Rev Clin Psychol.* 2020;16(1):187-212. https://doi.org/10.1146/annurev-clinpsy-050718-095744.
2. Cox WM, Klinger E. A motivational model of alcohol use. *J Abnorm Psychol.* 1988;97(2):168-180. https://doi.org/10.1037//0021-843x.97.2.168.
3. Cox WM, Klinger E, Fadardi JS. The motivational basis of cognitive determinants of addictive behaviors. *Addict Behav.* 2015;44:16-22. https://doi.org/10.1016/j.addbeh.2014.11.019.
4. Ditre JW, Brandon TH, Zale EL, Meagher MM. Pain, nicotine, and smoking: Research findings and mechanistic considerations. *Psychol Bull.* 2011;137(6):1065-1093. https://doi.org/10.1037/a0025544.
5. Ditre JW, Zale EL, LaRowe LR. A reciprocal model of pain and substance use: Transdiagnostic considerations, clinical implications, and future directions. *Annu Rev Clin Psychol.* 2019;15:503-528. https://doi.org/10.1146/annurev-clinpsy-050718-095440.
6. Zale EL, Maisto SA, Ditre JW. Interrelations between pain and alcohol: An integrative review. *Clin Psychol Rev.* 2015;37:57-71. https://doi.org/10.1016/j.cpr.2015.02.005.
7. Witkiewitz K, Vowles KE. Alcohol and opioid use, co-use, and chronic pain in the context of the opioid epidemic: A critical review. *Alcohol Clin Exp Res.* 2018;42(3):478-488. https://doi.org/10.1111/acer.13594.

8. Sauer-Zavala S, Gutner CA, Farchione TJ, Boettcher HT, Bullis JR, Barlow DH. Current definitions of "transdiagnostic" in treatment development: A search for consensus. *Behav Ther.* 2017;48(1):128-138. https://doi.org/10.1016/j.beth.2016.09.004.
9. LaRowe LR, Zvolensky MJ, Ditre JW. The role of anxiety-relevant transdiagnostic factors in comorbid chronic pain and tobacco cigarette smoking. *Cognit Ther Res.* 2019;43(1):102-113. https://doi.org/10.1007/s10608-018-9957-y.
10. Schiller JS, Lucas JW, Peregoy JA. Summary health statistics for U.S. adults: National Health Interview Survey, 2011. *Vital Health Stat.* 2012;10(256). https://www.cdc.gov/nchs/data/series/sr_10/sr10_256.pdf.
11. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration (SAMHSA). *Key Substance Use and Mental Health Indicators in the United States: Results From the 2015 National Survey on Drug Use and Health: Summary of National Findings.* (HHS Publication No. SMA 16-4984, NSDUH Series H-51). Rockville, MD: U.S. Department of Health and Human Services (HHS); 2015.
12. World Health Organization (WHO). *Lexicon of Alcohol and Drug Terms.* Geneva, Switzerland: WHO; 1994. https://apps.who.int/iris/bitstream/handle/10665/39461/9241544686_eng.pdf;jsessionid=F279F7BE406672A2B1CD6CAEA9927955?sequence=1.
13. Esser MB, Sherk A, Liu Y, et al. Deaths and years of potential life lost from excessive alcohol use—United States, 2011–2015. *MMWR Morb Mortal Wkly Rep.* 2020;69(30):981-987. https://doi.org/10.15585/mmwr.mm6930a1.
14. Centers for Disease Control and Prevention (CDC). *Alcohol and Public Health: Alcohol-Related Disease Impact (ARDI). Average for United States 2006–2010 Alcohol-Attributable Deaths Due to Excessive Alcohol Use.* Atlanta, GA: CDC; 2013.
15. Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD. 2010 national and state costs of excessive alcohol consumption. *Am J Prev Med.* 2015;49(5):e73-e79. https://doi.org/10.1016/j.amepre.2015.05.031.
16. CDC. *2018 Annual Surveillance Report of Drug-Related Risks and Outcomes—United States.* Atlanta, GA: HHS; August 2018. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf.
17. Lipari RN, Hughes A. How people obtain the prescription pain relievers they misuse. The CBHSQ Report: January 12, 2017. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2017. https://www.ncbi.nlm.nih.gov/books/NBK424785/.
18. Wilson N, Kariisa M, Seth P, Smith H, Davis NL. Drug and opioid-involved overdose deaths—United States, 2017–2018. *MMWR Morb Mortal Wkly Rep.* 2020;69(11):290-297. https://doi.org/10.15585/mmwr.mm6911a4.
19. Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. *Med Care.* 2016;54(10):901-906. https://doi.org/10.1097/mlr.0000000000000625.
20. Volkow ND, Wang G-J, Fowler JS, Tomasi D, Telang F. Addiction: Beyond dopamine reward circuitry. *Proc Natl Acad Sci U S A.* 2011;108(37):15037-15042. https://doi.org/10.1073/pnas.1010654108.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Arlington, VA: APA; 2013.
22. Earleywine M, Newcomb MD. Concurrent versus simultaneous polydrug use: Prevalence, correlates, discriminant validity, and prospective effects on health outcomes. *Exp Clin Psychopharmacol.* 1997;5(4):353-364. https://doi.org/10.1037/1064-1297.5.4.353.
23. Edwards KA, Vowles KE, Witkiewitz K. Co-use of alcohol and opioids. *Curr Addict Rep.* 2017;4(2):194-199. https://doi.org/10.1007/s40429-017-0147-x.
24. McCabe SE, Cranford JA, Boyd CJ, Teter CJ. Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. *Addict Behav.* 2007;32(3):562-575. https://doi.org/10.1016/j.addbeh.2006.05.022.
25. Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD. Substance use disorders in a primary care sample receiving daily opioid therapy. *J Pain.* 2007;8(7):573-582. https://doi.org/10.1016/j.jpain.2007.02.432.
26. Saffier K, Colombo C, Brown D, Mundt MP, Fleming MF. Addiction Severity Index in a chronic pain sample receiving opioid therapy. *J Subst Abuse Treat.* 2007;33(3):303-311. https://doi.org/10.1016/j.jsat.2006.12.011.
27. Saunders KW, Von Korff M, Campbell CI, et al. Concurrent use of alcohol and sedatives among persons prescribed chronic opioid therapy: Prevalence and risk factors. *J Pain.* 2012;13(3):266-275. https://doi.org/10.1016/j.jpain.2011.11.004.
28. Peacock A, Bruno R, Larance B, et al. Same-day use of opioids and other central nervous system depressants amongst people who tamper with pharmaceutical opioids: A retrospective 7-day diary study. *Drug Alcohol Depend.* 2016;166:125-133. https://doi.org/10.1016/j.drugalcdep.2016.07.003.
29. Saha TD, Kerridge BT, Goldstein RB, et al. Nonmedical prescription opioid use and DSM-5 nonmedical prescription opioid use disorder in the United States. *J Clin Psychiatry.* 2016;77(6):772-780. https://doi.org/10.4088/JCP.15m10386.
30. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health.* 1999;23(1):40-54.
31. Tori ME, Larochelle MR, Naimi TS. Alcohol or benzodiazepine co-involvement with opioid overdose deaths in the United States, 1999-2017. *JAMA Netw Open.* 2020;3(4):e202361. https://doi.org/10.1001/jamanetworkopen.2020.2361.
32. Cox JJ, Reimann F, Nicholas AK, et al. An SCN9A channelopathy causes congenital inability to experience pain. *Nature.* 2006;444(7121):894-898. https://doi.org/10.1038/nature05413.
33. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychol Bull.* 2007;133(4):581-624. https://doi.org/10.1037/0033-2909.133.4.581.
34. Turk DC, Melzack R. The measurement of pain and the assessment of people experiencing pain. In: Turk DC, Melzack R, eds. *Handbook of Pain Assessment.* New York, NY: The Guilford Press; 1992.
35. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain.* 2012;13(8):715-724. https://doi.org/10.1016/j.jpain.2012.03.009.
36. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain.* 2020;161(9):1976-1982. https://doi.org/10.1097/j.pain.0000000000001939.
37. Treede R-D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain.* 2015;156(6):1003-1007. https://doi.org/10.1097/j.pain.0000000000000160.
38. McMahon SB, Koltzenburg M, Tracey I, Turk DC. *Wall and Melzack's Textbook of Pain.* Philadelphia, PA: Saunders; 2013.
39. Institute of Medicine. Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, DC: National Academies Press; 2011.

40. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2018;67(36):1001-1006. https://doi.org/10.15585/mmwr.mm6736a2.
41. Vlaeyen JWS, Linton SJ. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain.* 2012;153(6):1144-1147. https://doi.org/10.1016/j.pain.2011.12.009.
42. Turk DC, Dworkin RH, Revicki D, et al. Identifying important outcome domains for chronic pain clinical trials: An *IMMPACT* survey of people with pain. *Pain.* 2008;137(2):276-285. https://doi.org/10.1016/j.pain.2007.09.002.
43. Von Korff M, Crane P, Lane M, et al. Chronic spinal pain and physical-mental comorbidity in the United States: Results from the national comorbidity survey replication. *Pain.* 2005;113(3):331-339. https://doi.org/10.1016/j.pain.2004.11.010.
44. LaRowe LR, Powers JM, Paladino MB, Ditre JW. Pain severity and alcohol use among daily tobacco cigarette smokers. *Am J Addict.* 2020;29(2):134-140. https://doi.org/10.1111/ajad.13003.
45. McDermott KA, Joyner KJ, Hakes JK, Okey SA, Cougle JR. Pain interference and alcohol, nicotine, and cannabis use disorder in a national sample of substance users. *Drug Alcohol Depend.* 2018;186:53-59. https://doi.org/10.1016/j.drugalcdep.2018.01.011.
46. Larson MJ, Paasche-Orlow M, Cheng DM, Lloyd-Travaglini C, Saitz R, Samet JH. Persistent pain is associated with substance use after detoxification: A prospective cohort analysis. *Addiction.* 2007;102(5):752-760. https://doi.org/10.1111/j.1360-0443.2007.01759.x.
47. Brennan PL, Schutte KK, Moos RH. Pain and use of alcohol to manage pain: Prevalence and 3-year outcomes among older problem and non-problem drinkers. *Addiction.* 2005;100(6):777-786. https://doi.org/10.1111/j.1360-0443.2005.01074.x.
48. Brennan PL, SooHoo S. Pain and use of alcohol in later life: Prospective evidence from the health and retirement study. *J Aging Health.* 2013;25(4):656-677. https://doi.org/10.1177/0898264313484058.
49. Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use correlates. *Drug Alcohol Depend.* 2008;94(1-3):38-47. https://doi.org/10.1016/j.drugalcdep.2007.09.018.
50. Bicket MC, Park JN, Torrie A, Allen ST, Weir BW, Sherman SG. Factors associated with chronic pain and non-medical opioid use among people who inject drugs. *Addict Behav.* 2020;102:106172. https://doi.org/10.1016/j.addbeh.2019.106172.
51. Evans TI, Liebling EJ, Green TC, Hadland SE, Clark MA, Marshall BDL. Associations between physical pain, pain management, and frequency of nonmedical prescription opioid use among young adults: A sex-specific analysis. *J Addict Med.* 2017;11(4):266-272. https://doi.org/10.1097/ADM.0000000000000318.
52. Amari E, Rehm J, Goldner E, Fischer B. Nonmedical prescription opioid use and mental health and pain comorbidities: A narrative review. *Can J Psychiatry.* 2011;56(8):495-502. https://doi.org/10.1177/070674371105600808.
53. Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: A multivariate analytical approach. *Pain.* 1996;68(1):157-167. https://doi.org/10.1016/s0304-3959(96)03162-4.
54. Zale EL, Maisto SA, Ditre JW. Anxiety and depression in bidirectional relations between pain and smoking: Implications for smoking cessation. *Behav Modif.* 2016;40(1-2):7-28. https://doi.org/10.1177/0145445515610744.
55. Baker TB, Piper ME, McCarthy DE, Majeskie MR, Fiore MC. Addiction motivation reformulated: An affective processing model of negative reinforcement. *Psychol Rev.* 2004;111(1):33-51. https://doi.org/10.1037/0033-295x.111.1.33.
56. Lerch MM, Albrecht E, Ruthenbürger M, Mayerle J, Halangk W, Krüger B. Pathophysiology of alcohol-induced pancreatitis. *Pancreas.* 2003;27(4):291-296. https://doi.org/10.1097/00006676-200311000-00003.
57. Chopra K, Tiwari V. Alcoholic neuropathy: Possible mechanisms and future treatment possibilities. *Br J Clin Pharmacol.* 2012;73(3):348-362. https://doi.org/10.1111/j.1365-2125.2011.04111.x.
58. Cheng Y, Macera CA, Davis DR, Ainsworth BE, Troped PJ, Blair SN. Physical activity and self-reported, physician-diagnosed osteoarthritis: Is physical activity a risk factor? *J Clin Epidemiol.* 2000;53(3):315-322. https://doi.org/10.1016/S0895-4356(99)00168-7.
59. Sá KN, Baptista AF, Matos MA, Lessa Í. Chronic pain and gender in Salvador population, Brazil. *Pain.* 2008;139(3):498-506. https://doi.org/10.1016/j.pain.2008.06.008.
60. Ditre JW, Zale EL, LaRowe LR, Kosiba JD, De Vita MJ. Nicotine deprivation increases pain intensity, neurogenic inflammation, and mechanical hyperalgesia among daily tobacco smokers. *J Abnorm Psychol.* 2018;127(6):578-589. https://doi.org/10.1037/abn0000353.
61. Ditre JW, Brandon TH. Pain as a motivator of smoking: Effects of pain induction on smoking urge and behavior. *J Abnorm Psychol.* 2008;117(2):467. https://doi.org/10.1037/0021-843X.117.2.467.
62. Dhingra LK, Homel P, Grossman B, et al. Ecological momentary assessment of smoking behavior in persistent pain patients. *Clin J Pain.* 2014;30(3):205-213. https://doi.org/10.1097/AJP.0b013e31829821c7.
63. Lawson PJ, Flocke SA. Teachable moments for health behavior change: A concept analysis. *Patient Educ Couns.* 2009;76(1):25-30. https://doi.org/10.1016/j.pec.2008.11.002.
64. Ferguson E, Zale E, Ditre J, et al. CANUE: A theoretical model of pain as an antecedent for substance use. *Ann Behav Med.* 2020;kaaa072. https://doi.org/10.1093/abm/kaaa072.
65. Sheu R, Lussier D, Rosenblum A, et al. Prevalence and characteristics of chronic pain in patients admitted to an outpatient drug and alcohol treatment program. *Pain Med.* 2008;9(7):911-917. https://doi.org/10.1111/j.1526-4637.2008.00420.x.
66. Goebel JR, Compton P, Zubkoff L, et al. Prescription sharing, alcohol use, and street drug use to manage pain among veterans. *J Pain Symptom Manage.* 2011;41(5):848-858. https://doi.org/10.1016/j.jpainsymman.2010.07.009.
67. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain.* 2015;156(4):569-576. https://doi.org/10.1097/01.j.pain.0000460357.01998.f1.
68. Cox WM, Klinger E. A motivational model of alcohol use: Determinants of use and change. In: Cox WM, Klinger E, eds. *Handbook of Motivational Counseling: Concepts, Approaches, and Assessment.* West Sussex, England: John Wiley & Sons, Ltd.; 2004:121-138.
69. Ditre JW, Zale EL, Heckman BW, Hendricks PS. A measure of perceived pain and tobacco smoking interrelations: Pilot validation of the pain and smoking inventory. *Cogn Behav Ther.* 2017;46(4):339-351. https://doi.org/10.1080/16506073.2016.1256347.

70. Larsen DK, Taylor S, Asmundson GJ. Exploratory factor analysis of the Pain Anxiety Symptoms Scale in patients with chronic pain complaints. *Pain.* 1997;69(1-2):27-34. https://doi.org/10.1016/S0304-3959(96)03232-0.
71. McCracken LM, Zayfert C, Gross RT. The Pain Anxiety Symptoms Scale: Development and validation of a scale to measure fear of pain. *Pain.* 1992;50(1):67-73. https://doi.org/10.1016/0304-3959(92)90113-P.
72. Sullivan MJ, Bishop SR, Pivik J. The pain catastrophizing scale: Development and validation. *Psychol Assess.* 1995;7(4):524-532. https://doi.org/10.1037/1040-3590.7.4.524.
73. Zale EL, LaRowe LR, Boissoneault J, Maisto SA, Ditre JW. Gender differences in associations between pain-related anxiety and alcohol use among adults with chronic pain. *Am J Drug Alcohol Abuse.* 2019;45(5):479-487. https://doi.org/10.1080/00952990.2019.1578968.
74. Ditre JW, Langdon KJ, Kosiba JD, Zale EL, Zvolensky MJ. Relations between pain-related anxiety, tobacco dependence, and barriers to quitting among a community-based sample of daily smokers. *Addict Behav.* 2015;42:130-135. https://doi.org/10.1016/j.addbeh.2014.11.032.
75. LaRowe LR, Langdon KJ, Zvolensky MJ, Zale EL, Ditre JW. Pain-related anxiety as a predictor of early lapse and relapse to cigarette smoking. *Exp Clin Psychopharmacol.* 2017;25(4):255-264. https://doi.org/10.1037/pha0000127.
76. Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behav Res Ther.* 1986;24(1):1-8. https://doi.org/10.1016/0005-7967(86)90143-9.
77. Schmidt NB, Buckner JD, Keough ME. Anxiety sensitivity as a prospective predictor of alcohol use disorders. *Behav Modif.* 2007;31(2):202-219. https://doi.org/10.1177/0145445506297019.
78. Rogers AH, Kauffman BY, Bakhshaie J, McHugh RK, Ditre JW, Zvolensky MJ. Anxiety sensitivity and opioid misuse among opioid-using adults with chronic pain. *Am J Drug Alcohol Abuse.* 2019;45(5):470-478. https://doi.org/10.1080/00952990.2019.1569670.
79. Asmundson GJ, Norton PJ, Veloso F. Anxiety sensitivity and fear of pain in patients with recurring headaches. *Behav Res Ther.* 1999;37(8):703-713. https://doi.org/10.1016/S0005-7967(98)00172-7.
80. Stewart SH, Asmundson GJ. Anxiety sensitivity and its impact on pain experiences and conditions: A state of the art. *Cogn Behav Ther.* 2006;35(4):185-188. https://doi.org/10.1080/16506070601090457.
81. Ocañez KL, McHugh RK, Otto MW. A meta-analytic review of the association between anxiety sensitivity and pain. *Depress Anxiety.* 2010;27(8):760-767. https://doi.org/10.1002/da.20681.
82. Zvolensky MJ, Rogers AH, Garey L, et al. The role of anxiety sensitivity in the relation between pain intensity with substance use and anxiety and depressive symptoms among smokers with chronic pain. *Int J Behav Med.* 2020;27(6):668-676. https://doi.org/10.1007/s12529-020-09914-4.
83. Simons JS, Gaher RM. The Distress Tolerance Scale: Development and validation of a self-report measure. *Motiv Emot.* 2005;29(2):83-102. https://doi.org/10.1007/s11031-005-7955-3.
84. Bornovalova MA, Gratz KL, Daughters SB, Hunt ED, Lejuez C. Initial RCT of a distress tolerance treatment for individuals with substance use disorders. *Drug Alcohol Depend.* 2012;122(1-2):70-76. https://doi.org/10.1016/j.drugalcdep.2011.09.012.
85. McHugh RK, Kneeland ET. Affective vulnerability in substance use disorders. *Curr Opin Psychol.* 2019;30:54-58. https://doi.org/10.1016/j.copsyc.2019.01.011.
86. LaRowe LR, Farris SG, Zvolensky MJ, Ditre JW. Associations between past-month pain and distress intolerance among daily cigarette smokers. *J Stud Alcohol Drugs.* 2018;79(5):781-789. https://doi.org/10.15288/jsad.2018.79.781.
87. Potter CM, Vujanovic AA, Marshall-Berenz EC, Bernstein A, Bonn-Miller MO. Posttraumatic stress and marijuana use coping motives: The mediating role of distress tolerance. *J Anxiety Disord.* 2011;25(3):437-443. https://doi.org/10.1016/j.janxdis.2010.11.007.
88. Semcho S, Bilsky SA, Lewis SF, Leen-Feldner EW. Distress tolerance predicts coping motives for marijuana use among treatment seeking young adults. *Addict Behav.* 2016;58:85-89. https://doi.org/10.1016/j.addbeh.2016.02.016.
89. Howell AN, Leyro TM, Hogan J, Buckner JD, Zvolensky MJ. Anxiety sensitivity, distress tolerance, and discomfort intolerance in relation to coping and conformity motives for alcohol use and alcohol use problems among young adult drinkers. *Addict Behav.* 2010;35(12):1144-1147. https://doi.org/10.1016/j.addbeh.2010.07.003.
90. Palfai TP, Taylor JL, Saitz R, Kratzer MPL, Otis JD, Bernstein JA. Development of a tailored, telehealth intervention to address chronic pain and heavy drinking among people with HIV infection: Integrating perspectives of patients in HIV care. *Addict Sci Clin Pract.* 2019;14(1):35. https://doi.org/10.1186/s13722-019-0165-1.
91. Nieto SJ, Green R, Grodin EN, Cahill CM, Ray LA. Pain catastrophizing predicts alcohol craving in heavy drinkers independent of pain intensity. *Drug Alcohol Depend.* 2021;218:108368. https://doi.org/10.1016/j.drugalcdep.2020.108368.
92. LaRowe LR, Maisto SA, Ditre JW. A measure of expectancies for alcohol analgesia: Preliminary factor analysis, reliability and validity. *Addict Behav.* 2021;116:106822. https://doi.org/10.1016/j.addbeh.2021.106822.
93. Moskal D, Maisto SA, De Vita M, Ditre JW. Effects of experimental pain induction on alcohol urge, intention to consume alcohol, and alcohol demand. *Exp Clin Psychopharmacol.* 2018;26(1):65-76. https://doi.org/10.1037/pha0000170.
94. Witkiewitz K, McCallion E, Vowles KE, et al. Association between physical pain and alcohol treatment outcomes: The mediating role of negative affect. *J Consult Clin Psychol.* 2015;83(6):1044-1057. https://doi.org/10.1037/ccp0000033.
95. Carpenter RW, Lane SP, Bruehl S, Trull TJ. Concurrent and lagged associations of prescription opioid use with pain and negative affect in the daily lives of chronic pain patients. *J Consult Clin Psychol.* 2019;87(10):872-886. https://doi.org/10.1037/ccp0000402.supp.
96. Finan PH, Carroll CP, Moscou-Jackson G, et al. Daily opioid use fluctuates as a function of pain, catastrophizing, and affect in patients with sickle cell disease: An electronic daily diary analysis. *J Pain.* 2018;19(1):46-56. https://doi.org/10.1016/j.jpain.2017.08.010.
97. Rogers AH, Bakhshaie J, Lam H, Langdon KJ, Ditre JW, Zvolensky MJ. Pain-related anxiety and opioid misuse in a racially/ethnically diverse young adult sample with moderate/severe pain. *Cogn Behav Ther.* 2018;47(5):372-382. https://doi.org/10.1080/16506073.2018.1436085.
98. Rogers AH, Kauffman BY, Garey L, Asmundson GJG, Zvolensky MJ. Pain-related anxiety among adults with obesity and chronic pain: Relations with pain, opioid misuse, and mental health. *Behav Med.* 2020;1-9. https://doi.org/10.1080/08964289.2020.1809337.

99. Rogers AH, Bakhshaie J, Zvolensky MJ, Vowles KE. Pain anxiety as a mechanism linking pain severity and opioid misuse and disability among individuals with chronic pain. *J Addict Med.* 2020;14(1):26-31. https://doi.org/10.1097/ADM.0000000000000538.
100. LaRowe LR, Chilcott LN, Zvolensky MJ, Vanable PA, Flood K, Ditre JW. Associations between pain-related anxiety, gender, and prescription opioid misuse among tobacco smokers living with HIV/AIDS. *Subst Use Misuse.* 2018;53(13):2210-2219. https://doi.org/10.1080/10826084.2018.1464028.
101. Lee SJ, Koussa M, Gelberg L, Heinzerling K, Young SD. Somatization, mental health and pain catastrophizing factors associated with risk of opioid misuse among patients with chronic non-cancer pain. *J Subst Abuse Treat.* 2020;25(4):357-362. https://doi.org/10.1080/14659891.2019.1704079.
102. Martel MO, Jamison RN, Wasan AD, Edwards RR. The association between catastrophizing and craving in patients with chronic pain prescribed opioid therapy: A preliminary analysis. *Pain Med.* 2014;15(10):1757-1764. https://doi.org/10.1111/pme.12416.
103. Arteta J, Cobos B, Hu Y, Jordan K, Howard K. Evaluation of how depression and anxiety mediate the relationship between pain catastrophizing and prescription opioid misuse in a chronic pain population. *Pain Med.* 2016;17(2):295-303. https://doi.org/10.1111/pme.12886.
104. Martel MO, Wasan AD, Jamison RN, Edwards RR. Catastrophic thinking and increased risk for prescription opioid misuse in patients with chronic pain. *Drug Alcohol Depend.* 2013;132(1-2):335-341. https://doi.org/10.1016/j.drugalcdep.2013.02.034.
105. Rogers AH, Shepherd JM, Orr MF, Bakhshaie J, McHugh RK, Zvolensky MJ. Exploring anxiety sensitivity in the relationship between pain intensity and opioid misuse among opioid-using adults with chronic pain. *J Psychiatr Res.* 2019;111:154-159. https://doi.org/10.1016/j.jpsychires.2019.02.004.
106. Smit T, Rogers AH, Garey L, Allan NP, Viana AG, Zvolensky MJ. Anxiety sensitivity and pain intensity independently predict opioid misuse and dependence in chronic pain patients. *Psychiatry Res.* 2020;294:113523. https://doi.org/10.1016/j.psychres.2020.113523.
107. Rogers AH, Garey L, Bakhshaie J, Viana AG, Ditre JW, Zvolensky MJ. Anxiety, depression, and opioid misuse among adults with chronic pain: The role of anxiety sensitivity. *Clin J Pain.* 2020;36(11):862-867. https://doi.org/10.1097/AJP.0000000000000870.
108. Rogers AH, Garey L, Raines AM, Allan NP, Schmidt NB, Zvolensky MJ. Anxiety sensitivity and opioid use motives among adults with chronic low back pain. *Exp Clin Psychopharmacol.* 2020. https://doi.org/10.1037/pha0000381.
109. Buckner JD, Keough ME, Schmidt NB. Problematic alcohol and cannabis use among young adults: The roles of depression and discomfort and distress tolerance. *Addict Behav.* 2007;32(9):1957-1963. https://doi.org/10.1016/j.addbeh.2006.12.019.
110. McHugh RK, Edwards R, Jamison R, Cornelius M, Weiss R. W174. Distress intolerance is associated with prescription opioid misuse in chronic pain patients. *Neuropsychopharmacology.* 2014;39:S585. https://doi.org/10.1038/npp.2014.282.
111. LaRowe LR, Powers JM, Garey L, Rogers AH, Zvolensky MJ, Ditre JW. Pain-related anxiety, sex, and co-use of alcohol and prescription opioids among adults with chronic low back pain. *Drug Alcohol Depend.* 2020;214:108171. https://doi.org/10.1016/j.drugalcdep.2020.108171.
112. Votaw VR, Witkiewitz K, Vowles KE, Weiss RD, Griffin ML, McHugh RK. Pain interference and catastrophizing are not associated with polysubstance use among treatment-seeking patients with substance use disorders and chronic pain. *Am J Drug Alcohol Abuse.* 2020;46(5):604-612. https://doi.org/10.1080/00952990.2020.1757687.
113. Wiech K, Tracey I. Pain, decisions, and actions: A motivational perspective. *Front Neurosci.* 2013;7:46. https://doi.org/10.3389/fnins.2013.00046.
114. Moskal D, Maisto SA, De Vita M, Ditre JW. Effects of experimental pain induction on alcohol urge, intention to consume alcohol, and alcohol demand. *Exp Clin Psychopharmacol.* 2018;26(1):65-76. https://doi.org/10.1037/pha0000170.
115. Zale EL, Ditre JW. Pain-related fear, disability, and the fear-avoidance model of chronic pain. *Curr Opin Psychol.* 2015;5:24-30. https://doi.org/10.1016/j.copsyc.2015.03.014.
116. Powers J, Heckman B, LaRowe L, Ditre J. Smokers with pain are more likely to report use of e-cigarettes and other nicotine products. *Exp Clin Psychopharmacol.* 2020;28(5):601-608. https://doi.org/10.1037/pha0000335.
117. Jobski K, Schmid U, Behr S, Andersohn F, Garbe E. 3-year prevalence of alcohol-related disorders in German patients treated with high-potency opioids. *Pharmacoepidemiol Drug Saf.* 2012;21(10):1125-1129. https://doi.org/10.1002/pds.3268.
118. Jones CM, Paulozzi LJ, Mack KA. Alcohol involvement in opioid pain reliever and benzodiazepine drug abuse–related emergency department visits and drug-related deaths—United States, 2010. *MMWR Morb Mortal Wkly Rep.* 2014;63(40):881-885. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6340a1.htm.
119. Park TW, Saitz R, Nelson KP, Xuan Z, Liebschutz JM, Lasser KE. The association between benzodiazepine prescription and aberrant drug-related behaviors in primary care patients receiving opioids for chronic pain. *Subst Abus.* 2016;37(4):516-520. https://doi.org/10.1080/08897077.2016.1179242.
120. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. *Pain Med.* 2016;17(1):85-98. https://doi.org/10.1111/pme.12907.
121. Leventhal AM, Zvolensky MJ. Anxiety, depression, and cigarette smoking: A transdiagnostic vulnerability framework to understanding emotion-smoking comorbidity. *Psychol Bull.* 2015;141(1):176-212. https://doi.org/10.1037/bul0000003.
122. Paulus DJ, Talkovsky AM, Heggeness LF, Norton PJ. Beyond negative affectivity: A hierarchical model of global and transdiagnostic vulnerabilities for emotional disorders. *Cogn Behav Ther.* 2015;44(5):389-405. https://doi.org/10.1080/16506073.2015.1017529.
123. Gallagher MW. Transdiagnostic mechanisms of change and cognitive-behavioral treatments for PTSD. *Curr Opin Psychol.* 2017;14:90-95. https://doi.org/10.1016/j.copsyc.2016.12.002.
124. Krueger RF, Eaton NR. Transdiagnostic factors of mental disorders. *World Psychiatry.* 2015;14(1):27-29. https://doi.org/10.1002/wps.20175.
125. Conroy DA, Arnedt JT. Sleep and substance use disorders: An update. *Curr Psychiatry Rep.* 2014;16(10):487. https://doi.org/10.1007/s11920-014-0487-3.
126. Husak AJ, Bair MJ. Chronic pain and sleep disturbances: A pragmatic review of their relationships, comorbidities, and treatments. *Pain Med.* 2020;21(6):1142-1152. https://doi.org/10.1093/pm/pnz343.

127. Brown SA, Christiansen BA, Goldman MS. The Alcohol Expectancy Questionnaire: An instrument for the assessment of adolescent and adult alcohol expectancies. *J Stud Alcohol.* 1987;48(5):483-491. https://doi.org/10.15288/jsa.1987.48.483.
128. McHugh RK, Votaw VR, Sugarman DE, Greenfield SF. Sex and gender differences in substance use disorders. *Clin Psychol Rev.* 2018;66:12-23. https://doi.org/10.1016/j.cpr.2017.10.012.
129. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley III JL. Sex, gender, and pain: A review of recent clinical and experimental findings. *J Pain.* 2009;10(5):447-485. https://doi.org/10.1016/j.jpain.2008.12.001.
130. American Psychological Association. *APA Dictionary of Psychology.* 2nd ed. Washington, DC: APA; 2015.
131. Keogh E, Boerner KE. Exploring the relationship between male norm beliefs, pain-related beliefs and behaviours: An online questionnaire study. *Eur J Pain.* 2020;24(2):423-434. https://doi.org/10.1002/ejp.1499.
132. Altemus M, Sarvaiya N, Epperson CN. Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol.* 2014;35(3):320-330. https://doi.org/10.1016/j.yfrne.2014.05.004.
133. Marmorstein NR. Relationships between anxiety and externalizing disorders in youth: The influences of age and gender. *J Anxiety Disord.* 2007;21(3):420-432. https://doi.org/10.1016/j.janxdis.2006.06.004.
134. Parent MC, Arriaga AS, Gobble T, Wille L. Stress and substance use among sexual and gender minority individuals across the lifespan. *Neurobiol Stress.* 2018;10:100146. https://doi.org/10.1016/j.ynstr.2018.100146.
135. Strath LJ, Sorge RE, Owens MA, et al. Sex and gender are not the same: Why identity is important for people living with HIV and chronic pain. *J Pain Res.* 2020;13:829-835. https://doi.org/10.2147/JPR.S248424.
136. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag.* 2012;2(3):219-230. https://doi.org/10.2217/pmt.12.7.
137. Lee P, Le Saux M, Siegel R, et al. Racial and ethnic disparities in the management of acute pain in US emergency departments: Meta-analysis and systematic review. *Am J Emerg Med.* 2019;37(9):1770-1777. https://doi.org/10.1016/j.ajem.2019.06.014.
138. Morales ME, Yong RJ. Racial and ethnic disparities in the treatment of chronic pain. *Pain Med.* 2021;22(1):75-90. https://doi.org/10.1093/pm/pnaa427.
139. Chartier K, Caetano R. Ethnicity and health disparities in alcohol research. *Alcohol Res Health.* 2010;33(1-2):152-160. https://pubs.niaaa.nih.gov/publications/arh40/152-160.pdf.
140. LaRowe LR, Rother Y, Powers JM, Zvolensky MJ, Vanable PA, Ditre JW. Pain self-efficacy, race, and motivation to quit smoking among persons living with HIV (PLWH). *Addict Behav.* 2020;105:106318. https://doi.org/10.1016/j.addbeh.2020.106318.
141. Baker TB, Mermelstein R, Collins LM, et al. New methods for tobacco dependence treatment research. *Ann Behav Med.* 2011;41(2):192-207. https://doi.org/10.1007/s12160-010-9252-y.
142. Mueser KT. *Integrated Treatment for Dual Disorders: A Guide to Effective Practice.* Guilford Press; 2003.
143. Zvolensky MJ, Garey L, Allan NP, et al. Effects of anxiety sensitivity reduction on smoking abstinence: An analysis from a panic prevention program. *J Consult Clin Psychol.* 2018;86(5):474-485. https://doi.org/10.1037/ccp0000288.
144. Worden BL, Davis E, Genova M, Tolin DF. Development of an anxiety sensitivity (AS) intervention for high-AS individuals in substance use disorders treatment. *Cognit Ther Res.* 2015;39(3):343-355. https://doi.org/10.1007/s10608-014-9666-0.
145. Leahy RL. *Cognitive Therapy: Basic Principles and Applications.* New York, NY: Jason Aronson, Incorporated; 1996.
146. Bailey KM, Carleton RN, Vlaeyen JW, Asmundson GJ. Treatments addressing pain-related fear and anxiety in patients with chronic musculoskeletal pain: A preliminary review. *Cogn Behav Ther.* 2010;39(1):46-63. https://doi.org/10.1080/16506070902980711.
147. Boswell JF, Farchione TJ, Sauer-Zavala S, Murray HW, Fortune MR, Barlow DH. Anxiety sensitivity and interoceptive exposure: A transdiagnostic construct and change strategy. *Behav Ther.* 2013;44(3):417-431. https://doi.org/10.1016/j.beth.2013.03.006.
148. Fernandez E, Turk DC. The utility of cognitive coping strategies for altering pain perception: A meta-analysis. *Pain.* 1989;38(2):123-135. https://doi.org/10.1016/0304-3959(89)90230-3.
149. Keefe FJ. Cognitive behavioral therapy for managing pain. *Clin Psychol (Aust Psychol Soc).* 1996;49(3):4-5. https://doi.org/10.1037/e555342011-002.
150. McCracken LM, Vowles KE. Acceptance and commitment therapy and mindfulness for chronic pain: Model, process, and progress. *Am Psychol.* 2014;69(2):178-187. https://doi.org/10.1037/a0035623.
151. Swift RM, Aston ER. Pharmacotherapy for alcohol use disorder: Current and emerging therapies. *Harv Rev Psychiatry.* 2015;23(2):122-133. https://doi.org/10.1097/hrp.0000000000000079.
152. Nona CN, Hendershot CS, Le Foll B. Effects of cannabidiol on alcohol-related outcomes: A review of preclinical and human research. *Exp Clinical Psychopharmacol.* 2019;27(4):359-369. https://doi.org/10.1037/pha0000272.
153. Kranzler HR, Feinn R, Morris P, Hartwell EE. A meta-analysis of the efficacy of gabapentin for treating alcohol use disorder. *Addiction.* 2019;114(9):1547-1555. https://doi.org/10.1111/add.14655.
154. Carrà G, Crocamo C, Humphris G, et al. Engagement in the Overdose RIsk InfOrmatioN (ORION) e-health tool for opioid overdose prevention and self-efficacy: A preliminary study. *Cyberpsychol Behav Soc Netw.* 2017;20(12):762-768. https://doi.org/10.1089/cyber.2016.0744.
155. Huhn AS, Garcia-Romeu AP, Dunn KE. Opioid overdose education for individuals prescribed opioids for pain management: Randomized comparison of two computer-based interventions. *Front Psychiatry.* 2018;9:34. https://doi.org/10.3389/fpsyt.2018.00034.
156. Egli M, Koob GF, Edwards S. Alcohol dependence as a chronic pain disorder. *Neurosci Biobehav Rev.* 2012;36(10):2179-2192. https://doi.org/10.1016/j.neubiorev.2012.07.010.
157. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: Evidence and recommendations for everyday practice. *Mayo Clin Proc.* 2015;90(6):828-842. https://doi.org/10.1016/j.mayocp.2015.04.003.
158. McCaul KD, Hockemeyer JR, Johnson RJ, Zetocha K, Quinlan K, Glasgow RE. Motivation to quit using cigarettes: A review. *Addict Behav.* 2006;31(1):42-56. https://doi.org/10.1016/j.addbeh.2005.04.004.
159. Zale EL, Maisto SA, De Vita MJ, Hooten WM, Ditre JW. Increasing cessation motivation and treatment engagement among smokers in pain: A pilot randomized controlled trial. *Exp Clin Psychopharmacol.* 2020. https://doi.org/10.1037/pha0000424.
160. Hooten WM, LaRowe LR, Zale EL, Ditre JW, Warner DO. Effects of a brief pain and smoking cessation intervention in adults with chronic pain: A randomized controlled trial. *Addict Behav.* 2019;92:173-179. https://doi.org/10.1016/j.addbeh.2018.11.040.

161. Powers JM, Zvolensky MJ, Ditre JW. An integrative review of personalized feedback interventions for pain and alcohol. *Curr Opin Psychol.* 2019;30:48-53. https://doi.org/10.1016/j.copsyc.2019.01.013.
162. Bandura A. Social cognitive theory and exercise of control over HIV infection. In: DiClemente RJ, Peterson JL, eds. *Preventing AIDS.* Springer; 1994:25-59. https://doi.org/10.1007/978-1-4899-1193-3_3.
163. Miller WR, Rollnick S. *Preparing People for Change.* New York, NY: Guilford Press; 2002.
164. Kristjánsdóttir ÓB, Fors EA, Eide E, et al. A smartphone-based intervention with diaries and therapist feedback to reduce catastrophizing and increase functioning in women with chronic widespread pain. Part 2: 11-month follow-up results of a randomized trial. *J Med Internet Res.* 2013;15(3):e72. https://doi.org/10.2196/jmir.2442.
165. Nes AA, van Dulmen S, Wicksell R, Fors EA, Eide H. Analyzing change processes resulting from a smartphone maintenance intervention based on acceptance and commitment therapy for women with chronic widespread pain. *Int J Behav Med.* 2017;24(2):215-229. https://doi.org/10.1007/s12529-016-9590-7.
166. Riper H, Spek V, Boon B, et al. Effectiveness of e-self-help interventions for curbing adult problem drinking: A meta-analysis. *J Med Internet Res.* 2011;13(2):e42. https://doi.org/10.2196/jmir.1691.
167. Kuerbis AN, Hail L, Moore AA, Muench FJ. A pilot study of online feedback for adult drinkers 50 and older: Feasibility, efficacy, and preferences for intervention. *J Subst Abuse Treat.* 2017;77:126-132. https://doi.org/10.1016/j.jsat.2017.04.004.
168. Ditre JW, LaRowe LR, Vanable PA, De Vita MJ, Zvolensky MJ. Computer-based personalized feedback intervention for cigarette smoking and prescription analgesic misuse among persons living with HIV (PLWH). *Behav Res Ther.* 2019;115:83-89. https://doi.org/10.1016/j.brat.2018.10.013.
169. Nes AAG, Eide H, Kristjánsdóttir ÓB, van Dulmen S. Web-based, self-management enhancing interventions with e-diaries and personalized feedback for persons with chronic illness: A tale of three studies. *Patient Educ Couns.* 2013;93(3):451-458. https://doi.org/10.1016/j.pec.2013.01.022.
170. Nahum-Shani I, Hekler EB, Spruijt-Metz D. Building health behavior models to guide the development of just-in-time adaptive interventions: A pragmatic framework. *Health Psychol.* 2015;34s(0):1209-1219. https://doi.org/10.1037/hea0000306.